Infections/Inflammation of the GU Tract: Interstitial Cystitis
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EFFECT OF IP-751, AJULEMIC ACID, AGAINST ACETIC ACID INDUCED BLADDER PAIN RESPONSES IN RATS 24H AFTER INTRAVESICAL ADMINISTRATION

Ratna Ganabathi, Pradeep Tyagi, Fernando De Miguel, Shachi Tyagi, Naoki Yoshimura, Michael B Chancellor, Pittsburgh, PA*

Introduction and Objective: Ajulemic acid (IP-751) is a potent analog of tetrahydrocannabinol (THC)-11-oic acid, which is a major metabolite of THC, the principal psychotropic constituent of Cannabis. Studies on isolated tissue strips of various species have shown inhibitory role of CB agonists on neuronally evoked contractions of bladder. Thus, we hypothesized that IP751 is effective to suppress urinary frequency and bladder pain responses in bladder hypersensitive disorders such as interstitial cystitis. The aqueous insolublity of Ajulemic acid (cannabinoid receptor agonist IP-751) prompted its formulations into liposomes for its evaluation after intravesical administration to determine the duration of biological activity against acute bladder irritation induced in rats. Methods: The cannabinoid agonist IP-751 was formulated into liposomes with lipid and drug in 2:1 molar ratio and a final drug concentration of 0.8mg/ml. Female Sprague Dawley rats were instilled 0.5ml of either saline or liposomal IP-751 for 30min under halothane anesthesia. Liposomes in absence of drug were also instilled in control rats. 24h after instillation, continuous cystometrograms were performed under urethane anesthesia by filling the bladder (0.04 ml per min) with saline, followed by 0.125% acetic acid. Decrease in intercontraction intervals (ICI) of each rat by acetic acid over its baseline value was calculated as percent reduction. Results: Rats instilled with saline 24h earlier showed a decrease in ICI after intravesical instillation of acetic acid (83$\pm$6.4% decrease, n=5). However, rats instilled with liposomal IP-751 showed a significantly decreased response (percent decrease of ICI 24.7$\pm$ 6.4%, n=5) to acetic acid infusion ($p<0.05$, unpaired t-test) as compared to control groups. Rats instilled with inert liposomes devoid of drug showed ICI similar to saline treated rats. Conclusions: This is the first report evaluating the effect of a cannabinoid agonist after intravesical administration. Liposomal formulation of IP-751 can suppress bladder nociceptive responses induced by bladder irritation. A 30 minute instillation has sustained biological activity of at least 24 hours. Liposome can effectively deliver hydrophobic drugs such as IP-751 and further studies are warranted to determine the mechanism of its action by this new route of administration. Intravesical liposomal formulation of ajulemic acid may be a promising treatment in patients with painful bladder syndrome/interstitial cystitis.

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