

LAMIVUDINE-ARTESUNATE CO ADMINISTRATION ALTERS PIROXICAM MEDIATED ANALGESIA IN MICE

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SUMMARY

Lamivudine-Artesunate co-administration is common in HIV-malaria settings, as well as in prophylaxis for occupational HIV exposure and presumptive malaria treatment. Pain is a symptom often associated with malaria and HIV which is usually treated with piroxicam due to availability, affordability, and low addiction potential. This study evaluated possible analgesic effects of lamivudine and artesunate, and also the effect of lamivudine-artesunate co-administration on piroxicam mediated analgesia in mice using acetic acid induced writhing method. Animals received 21 day intraperitoneal treatments with vehicle, lamivudine, artesunate or lamivudine/artesunate co administration. The result showed that artesunate possessed analgesic properties, and that piroxicam mediated analgesia was significantly reduced ($p < 0.05$) in the presence of concomitant lamivudine-artesunate treatment. This data suggests the need for caution and possible alternate analgesics while on lamivudine-artesunate therapy in order to effectively alleviate pain, when this is desired with lamivudine-artesunate co administration.

KEY WORDS: Analgesic, Artesunate, Drug Interaction, Lamivudine, Pain

INTRODUCTION

Malaria has remained a serious public health concern in several countries of the world¹, and is one of the oldest and most prevalent infectious diseases². Estimates conservatively put the mortality from malaria between 1-2 million annually, majority of whom are children below the age of five and pregnant women. Much effort to eradicate the disease in endemic areas has been largely unsuccessful despite several programs and campaigns that have been mounted in the past. The

control/elimination of malaria has remained a problem due to *falciparum* resistance to drugs that have been previously used for over fifty years, and this has led to the introduction and advocacy of Artemisinin Combination Therapy (ACT) by the World Health Organization³. Artesunate is the most important of the derivatives of artemisinin in use⁴, and is used in a large number of ACTs.

While malaria continues to ravage much of tropical Africa, the problem of HIV is another major medical challenge with over 70% of global HIV population

estimated to reside in sub Saharan Africa⁵. Highly active anti retroviral therapy (HAART), which had been previously expensive and in short supply have become largely available due to global interventions and the provision of cheaper generic medications. Lamivudine is one of the first line medications employed in HAART regimens⁶, post exposure prophylaxis⁷, treatment of Hepatitis B virus infection⁸ and prevention of mother to child transmission in combination with zidovudine⁹. Due to the endemic nature of malaria which infects adults on the average five times annually, the concurrent use of lamivudine and artesunate presents a potential drug-drug interaction. In association with malaria and HIV, are various pain syndromes such as acute pancreatitis, which is sometimes a complication in malaria¹⁰. Piroxicam is commonly used due to its availability, low cost and low addiction potential. This study was conducted to investigate the possible effect of lamivudine-artesunate co-administration on piroxicam mediated analgesia in mice using a chemically induced pain model.

Materials and Methods

Animals: Albino mice of either sex weighing 26-32 grams were obtained from the Animal House of the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria. The animals were housed in aluminium cages and maintained with standard feed and water *ad libitum*. The animals were used in accordance with the National Animal Welfare guidelines and all drugs were administered intraperitoneally *Grouping and treatment protocol*

In the first phase of the study, twenty five mice were divided into five groups of five

mice each. To evaluate the possible effect of acute single time administration of the drugs and combination on acetic acid induced writhes, animals received either saline (10 ml/kg), lamivudine (20 mg/kg), artesunate (10 mg/kg) or a combination of lamivudine and artesunate, while another group received piroxicam (5mg/kg) as standard. All animals were challenged with 10 ml/kg of 0.75 % acetic acid solution thirty minutes after the group treatments, and the total number of writhes over a twenty minute duration was recorded according to a previously described method¹¹.

The second phase of the study was conducted in order to determine the effect of sub acute lamivudine-artesunate administration on piroxicam mediated analgesia, over a twenty one day total drug treatment period. Animals were divided into five groups of five mice. Animals received saline (10 ml/kg), lamivudine (20 mg/kg), artesunate (10 mg/kg) or a combination of lamivudine and artesunate, while another group received piroxicam (5 mg/kg) as standard. Animals that were placed on lamivudine received 20 mg/kg for 21 days while those that received artesunate were treated from day 15-21 of the study. On day 15, which was the first day of co administration of lamivudine and artesunate, all animals were challenged with acetic acid as previously described. However, all animals apart from the vehicle control received piroxicam (5 mg/kg) thirty minutes before the acetic acid challenge in addition to their respective group treatments. The number of writhes over a twenty minute duration was recorded. Drug treatment continued up till day 21 at which time the animals were again challenged with acetic acid thirty minutes after piroxicam treatment.

Preparation of Drugs

Artesunate was prepared by dissolving 60 mg in 1 ml 5% sodium bicarbonate and made up to 6 ml with normal saline. Lamivudine was dissolved with distilled water to desired concentrations.

Statistical Analysis

The data obtained from the study was analysed using one way ANOVA followed by Dunnett's post-hoc test and data are presented in mean \pm standard error of the mean, and $p < 0.05$ was considered statistically significant.

Discussion

Both lamivudine and artesunate were evaluated for peripherally mediated analgesia. Artesunate demonstrated significant analgesic property ($p < 0.05$) compared to vehicle control in the acetic acid induced writhing model (Figure 1). The effect exhibited was inhibited in the presence of lamivudine, although the mechanism by which this occurred is not currently known. Inhibition of acetic acid induced writhing has been used to evaluate peripherally mediated analgesia^{12,13}, and thus it may be possible that artesunate possesses peripherally mediated analgesia although centrally acting drugs have been known to inhibit acetic acid induced writhing. Non steroidal anti inflammatory drugs such as piroxicam act by inhibiting cyclooxygenase which acts on arachidonic acid to produce various prostaglandins and some other pain mediators¹⁴. NSAIDs have traditionally been utilized in the treatment of different types of acute and chronic pain¹⁵. Although pain is often a consequence of inflammation and is implicated in several clinical conditions,

sometimes pain results from previously non algogenic stimuli¹⁶. At the dose levels used in this study, the analgesic effect of piroxicam was attenuated by 3TC-AS co-administration as well as with the administration of either drug both on day 14 (Figure 2), and also on day 21 (Figure 3) of the drug treatment. Attenuation of piroxicam mediated analgesia was more evident in the 3TC-AS group than in the group that was treated with AS only. Conditions thus requiring such drug combinations including in HIV/malaria co administration may thus be affected. Various pain syndromes which are diverse in etiology and nature are encountered by HIV patients¹⁷. These include neuropathic pain, visceral pain, headaches and joint pains. In mild to moderate pain, non steroidal anti inflammatory drugs have been traditionally utilized as a therapeutic option. Also, in children, a study has shown the effectiveness of oral piroxicam in the management of osteoarticular painful attack in sickle cell anaemia¹⁸. In either case, the concurrent use of lamivudine and/artesunate is expedient and thus requisite analgesic management with piroxicam alongside underlying concurrent drug therapy may result in diminished analgesia. The clinical consequence of this situation is a likely downward shift in the outcome of pain management in patients who receive any combination of these drugs or individual drugs either as prophylactic agent or for disease management. Although it is not certain if this alteration in analgesic activity occurs via pharmacokinetic or pharmacodynamic mechanisms, it may be expedient to exercise caution and monitor response to pain therapy while on these concurrent medications in clinical settings.

Conclusion

This study has shown that artesunate possesses analgesic activity which is likely to be peripherally mediated. The study has also shown that piroxicam mediated analgesia is inhibited in the presence of lamivudine, artesunate or the combination of both drugs on an acute and sub-acute basis. This may be as a result of pharmacokinetic or pharmacodynamic interactions. The outcome of the current study therefore presents reason to further investigate the possible consequences of disease states on the analgesic effect of piroxicam in the presence of lamivudine and artesunate.

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Results

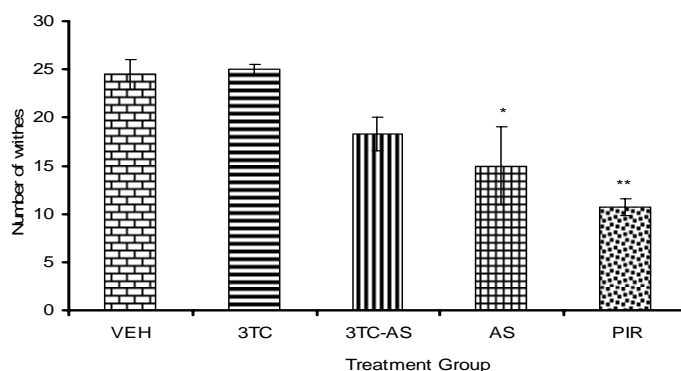


Figure 1: Effect of Acute 3TC-AS Co-administration on Acetic Acid-induced Writhes in Mice

Figure shows mean \pm SEM (n=5). (ANOVA followed by Dunnett's post hoc test. *= $P < .05$, **= $P < .01$ compared with VEH) VEH=vehicle, 3TC=lamivudine, AS=artesunate, PIR=piroxicam

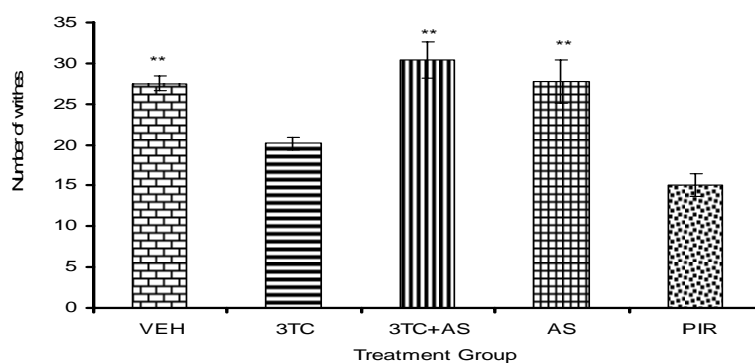


Figure 2: Effect of 3TC-AS on Piroxicam-mediated Analgesia in Healthy Mice on day 15

Figure shows mean \pm SEM (n=5). (ANOVA followed by Dunnett's post hoc test. *= $P < .05$, **= $P < .01$ when compared against PIR) VEH=vehicle, 3TC=lamivudine, AS=artesanate, PIR=piroxicam

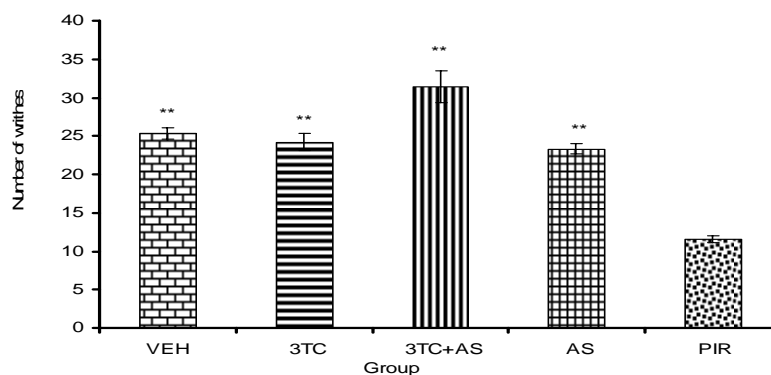


Figure 3: Effect of 3TC+AS on Piroxicam-mediated Analgesia in Healthy Mice on Day 21

Figure shows mean \pm SEM (n=5). (ANOVA followed by Dunnett's post hoc test. *= $P < .05$, **= $P < .01$ compared with PIR) VEH=vehicle, 3TC=lamivudine, AS=artesanate, PIR=piroxicam