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***SCIENTIFIC ARTICLE***

# Efeito Analgésico de Antagonistas do Receptor da Histamina $H_1$ em Modelo de Dor Provocada por Formalina em Ratos *

## *Analgesic Effects of $H_1$ Receptor Antagonists in the Rat Model of Formalin-Induced Pain*

*Hazem Adel Ashmawi, TSA [1], Leandro Mamede Braun, TSA [2], Angela Maria Sousa, TSA [3], Irimar de Paula Posso, TSA [4]*

**RESUMO**

Ashmawi HA, Braun LM, Sousa AM, Posso IP - Efeito Analgésico de Antagonistas do Receptor da Histamina $H_1$ em Modelo de Dor Provocada por Formalina em Ratos.

***JUSTIFICATIVA E OBJETIVOS****: Os receptores de histamina mediam vias nociceptivas principalmente no sistema nervoso central. Alguns estudos mostraram efeito analgésico de antagonistas de receptor de histamina no sistema nervoso periférico. Não está claro se o efeito analgésico local é classe específico ou droga específico.*

***MÉTODO****: Para responder a essa questão, utilizamos três diferentes antagonistas do receptor $H_1$ (pirilamina, prometazina e cetirizina) administrados diretamente na pata do rato, pela via intraperitoneal ou por bloqueio de nervo periférico em modelo de dor induzida por formalina. Observamos o efeito das drogas no comportamento do número de elevações da pata.*

***RESULTADOS****: Na fase I, a pirilamina local diminuiu o número de elevações da pata de forma dose-dependente. Na dose mais alta, a diminuição foi de 97,8%. Para a prometazina, a diminuição foi de 92% e para cetizirina, 23,9%. Na fase II, a pirilamina diminuiu o número de elevações da pata em 93,5%, a prometazina em 78,2% e a cetirizina em 80,1%. A administração dos fármacos por via intraperitoneal não alterou o comportamento doloroso. Quando utilizadas para bloqueio de nervo periférico, na fase I, a pirilamina diminuiu o número de elevações da pata em 96,7%, a prometazina em 73,3% e a cetirizina em 23,9%. Na fase II, a pirilamina levou à diminuição de 86,6%, a prometazina de 64,4% e a cetirizina de 19,9%.*

***CONCLUSÕES****: Os resultados mostraram que os antagonistas de receptor da histamina $H_1$ apresentam efeitos analgésicos locais, diferentes do efeito sistêmico, sendo um deles anti-inflamatório e classe específico e o outro específico para prometazina e pirilamina, semelhante a efeito clínico anestésico local.*

**Unitermos:** ANIMAIS: ratos; DOR, Experimental: formalina; DROGAS: cetirizina; pirilamina; prometazina.

**SUMMARY**

Ashmawi HA, Braun LM, Sousa AM, Posso IP – Analgesic Effects of $H_1$ Receptor Antagonists in the Rat Model of Formalin-induced Pain.

***BACKGROUND AND OBJECTIVES:*** *Histamine receptors mediate nociceptive pathways, especially in the central nervous system. Some studies have demonstrated the analgesic effects of histamine receptor antagonists in the peripheral nervous system. It is not clear whether the local analgesic effect is class-specific or drug-specific.*

***METHODS:*** *To answer this question, we used three different $H_1$ receptor antagonists (pyrilamine, promethazine, and cetirizine) administered directly in the paw of the rat, intraperitoneally, or in peripheral nerve blockade in the formalin-induced pain model. The effects of the drugs on the number of paw elevations were observed.*

***RESULTS:*** *In phase I, the local administration of pyrilamine caused a dose-dependent reduction on the number of paw elevations; in the highest dose, the number of paw elevations was reduced by 97.8%. Promethazine decreased it by 92%, while cetirizine decreased by 23.9%. In phase II, pyrilamine decreased the number of paw elevations by 93.5%, promethazine by 78.2%, and cetirizine by 80.1%. Intraperitoneal administration of drugs did not change painful behavior. When used in peripheral nerve block, in phase I pyrilamine reduced the number of paw elevations by 96.7%, promethazine by 73.3%, and cetirizine by 23.9%. In phase II, pyrilamine reduced the number of paw elevations by 86.6%, promethazine by 64.4%, and cetirizine by 19.9%.*

***CONCLUSIONS:*** *The results demonstrate that $H_1$ receptor antagonists have local analgesic effects, different from the systemic effects, one of them an anti-inflammatory and class-specific effect and the other similarly to the local anesthetic effect, specific for promethazine and pyrilamine*

**Keywords:** ANIMALS: rats; DRUGS: cetirizine, promethazine, pyrilamine; PAIN, Experimental: formalin.

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# *Analgesic Effects of $H_1$ Receptor Antagonists in the Rat Model of Formalin-Induced Pain*

Hazem Adel Ashmawi, TSA, M.D. [1], Leandro Mamede Braun, TSA, M.D. [2], Angela Maria Sousa, TSA, M.D. [3], Irimar de Paula Posso, TSA, M.D. [4]

## INTRODUCTION

Since the last century it has been known that histamine, present in the majority of cells, is a pain mediator. It activates polymodal nociceptors and produces pain when injected in the human skin. Tissue damage releases histamine causing local pain, vasodilation, and edema [1]. The actions of histamine are mediated by at least four pharmacologically distinct receptors members of the family of G-protein-coupled receptors. $H_1$ receptors are expressed in the brain, endothelial cells and smooth muscle cells. Contraction of the smooth muscle and an increase in vascular permeability are the main actions of $H_1$ receptors [2]. $H_2$ receptors play a major role in the modulation of gastric acid secretion, and $H_2$ receptor antagonists are widely used in the treatment of gastrointestinal ulcers [3]. $H_3$ receptors are located in nerve endings and body of histaminergic neurons in the tuberomamilar nucleus of the hypothalamus. They inhibit $Ca^{2+}$ conductance, decreasing neuronal depolarization and histamine release. $H_4$ receptors are very similar to $H_3$ receptors, but they are expressed in the hematopoietic cell line, especially eosinophils, mast cells, and basophils [5]. Very little is known on the biologic role of $H_4$ receptors. A role in inflam-

mation has been postulated since they are limited to hematopoietic cells [6].

The role of histamine in pain is different in the central and peripheral nervous systems. Central histamine has both pro- and anti-nociceptive actions. Histamine increases the central pain threshold [7,8]. $H_2$ receptors seem to be anti-nociceptive [9], while $H_1$ receptors are pro-nociceptive [8,10]. Proposed mechanisms for the analgesic action of $H_1$ receptors involve a supraspinal action on pre-synaptic receptors [8] located on the dorsal raphe nucleus or around the periaqueductal gray matter [11]. $H_2$ receptor antagonists such as famotidine and lupitidine showed antinociceptive actions when used systemically [12]. Although widely expressed in the central nervous system, $H_3$ receptors do not seem to be involved in pain modulation [13]. Peripheral histamine is involved in the stimulation of nociceptive fibers, and its antagonists show antinociceptive effects whose study has been neglected. Pyrilamine and cimetidine showed analgesic effects after the injection of formalin in the paw of rats [14,15]. However, it is not clear whether this effect is class- ($H_1$ receptor antagonist) or drug-specific.

The objective of this study was to evaluate the analgesic effects of three $H_1$ receptor antagonists – promethazine (derived from propilamine), cetirizine (derived from piperazine), and pyrilamine (derived from aminopyridine) – injected in the paw or in peripheral nerve block in the formalin-induced pain model in rats.

## METHODS

Wistar male rats weighing 280 to 350 g from the Biotério Central da Faculdade de Medicina da Universidade de São Paulo were used in all experiments. Animals had free access to water and food, and they were exposed to a light-dark cycle of 12 hours each. The study was approved by the Ethics Committee for Analysis of Research Projects of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and according to the directives for experimental pain investigation of the International Association for the Study of Pain (IASP) [16,17]. All experiments were performed between 9 a.m. and 3 p.m.

Pain was induced by the injection of 1% formalin (50 µL) on the dorsal aspect of the right posterior paw. Before the injection, animals were placed in a transparent plastic observation chamber for 20 minutes for acclimation. The rats were then removed for the administration of the drug and returned to the observation chamber. A mirror was placed behind the chamber to facilitate the visualization of paw elevations when it was out of the visual field of the observer. Rats were observed for 45 minutes after the administration of formalin. The number of paw elevations was quantified every five minutes. All movements not associated with locomotion, varying from subtle elevation or contraction of the thigh musculature to more vigorous paw movements, were considered paw elevation. Elevations were easy to observe and quantify [14,15,18-20].

Paw elevation was divided in phase I (0 to 10 minutes) and phase II (11 to 45 minutes), as previously described [18,19,21]. In the first part of the study, 65 animals were divided in groups of five rats each: the form group (receiving 50 µL of 1% formalin in the dorsal aspect of the right posterior paw) was used as positive control. Three different doses of each drug were injected always in association with 1% formalin for a final volume of 50 µL in the paw of the animal. The following doses were used: 0.05 µmol (pyr- 0.05, pro-0.05, cet- 0.05), 0.25 µmol (pyr- 0.25, pro-0.25, cet-0.25), and 1 µmol (pyr- 1, pro- 1, cet- 1). For the intraperitoneal route, 4 $\mu mol.kg^{-1}$ for a final volume of 200 µL were used; 50 µL of 1% formalin were injected in the paw.

The second part of the study was undertaken to evaluate the local analgesic effect of $H_1$ receptor antagonists through the sensitive blockade of the dorsal aspect of the paw. The drugs were injected to block the deep and superficial fibular nerves, responsible for the innervation of the dorsal region of the paw [22]. A dose of 5 µmol, at a volume of 50 µL, was injected in the heel ten minutes before the administration of 50 µL of 1% formalin in the paw. The groups were as follows: pyr-block, pro-block, cet-block, and lido-block (dose – 1.85 µmol); the lidocaine (lido-block) and formalin (form) groups were the controls. A higher dose was used in the nerve block than in the local dose (infiltrative) because a higher dose of the local anesthetic was necessary to block the nerve than that used to block free nerve endings, such as in infiltrative anesthesia.

Pyrilamine chloride was supplied by Sigma-Aldrich Pharmaceuticals, USA; promethazine chloride by Aventis-Pharma, Brazil; cetirizine chloride by Solvat Pharmaceuticals, Brazil; and lidocaine by Cristália Prod. Quim. Farm., Brazil.

Analysis of Variance (ANOVA) with a fixed factor followed by Tukey's multiple comparison procedure was used to analyze the data. Logarithmic transformation was used to stabilize variance in the different groups. Since in some situations the number of paw elevations was zero 0.7 was added to the value of the parameter before calculating the logarithm. In the second part of the study the Kruskal-Wallis test was used to analyze the number of paw elevations in phases I and II in the different groups. It was not possible to use parametric tests because the variability of the data was not the same in all groups even after the transformation. When the Kruskal-Wallis test indicated the presence of intergroup differences, Dunnett multiple comparisons was used.

## RESULTS

Figures 1A, 1B, and 1C show the evolution of the number of paw elevations after the administration of formalin in the different groups. In phase I, pyrilamine and promethazine decreased the number of paw elevations; all three doses of promethazine caused a similar decrease in elevation; and

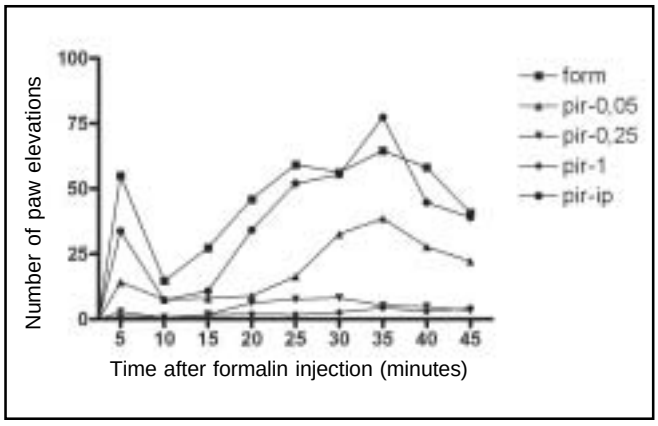


Figure 1A – Effects of Different Doses of Pyrilamine, Administered in Different Sites, on the Number of Paw Elevations. The local administration of pyrilamine showed a dose-dependent reduction in the number of paw elevations. The blockade was almost complete in the pyr-0.25 and pyr-1 groups. Intraperitoneal pyrilamine did not show anesthetic effects.

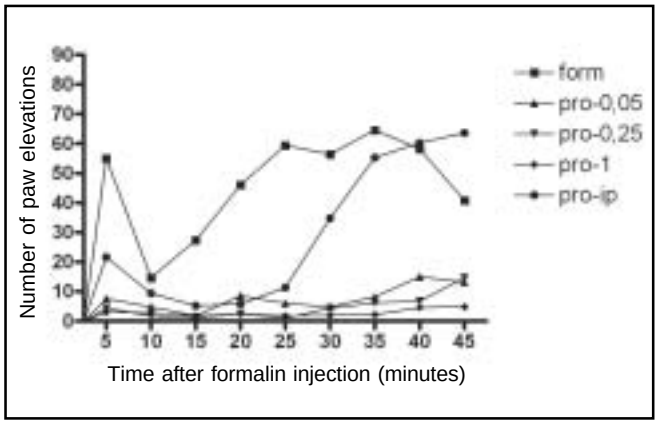


Figure 1B – Effects of Different Doses of Promethazine, Administered in Different Sites, on the Number of Paw Elevations. The local administration of promethazine showed a dose-dependent reduction in the number of paw elevations in phases I and II. The blockade was almost complete in the pro-0.25 and pro-1 groups. Intraperitoneal promethazine did not show analgesic effects.

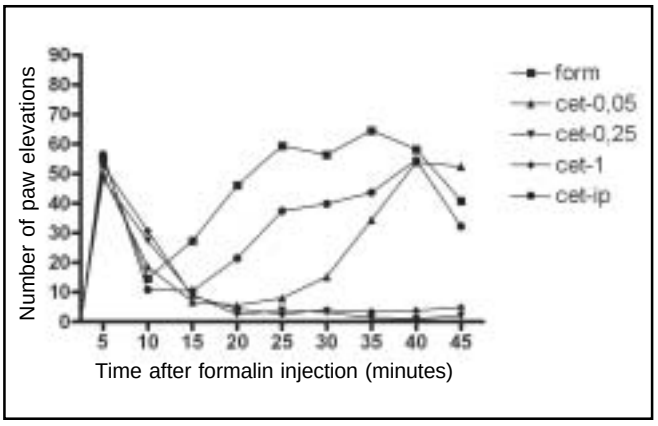


Figure 1C – Effects of Different Doses of Cetirizine, Administered in Different Sites, on the Number of Paw Elevations. The local administration of cetirizine showed a dose-dependent reduction in the number of paw elevations in phase II. The blockade was almost complete in the cet-0.25 and cet-1 groups. Cetirizine did not show analgesic effects in phase I or after intraperitoneal administration.

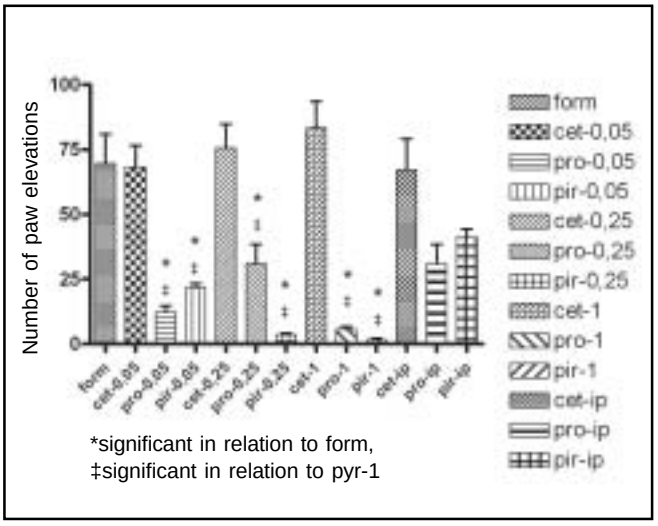


Figure 2A – Effects of the Local or Intraperitoneal Administration of $H_1$ Receptor Antagonists on the Number of Paw Elevations in Phase I. Higher doses (0.25 and 1 µmol) of pyrilamine and promethazine blocked phase I, but not cetirizine or when the drugs were administered intraperitoneally. Results shown as mean ± standard error, $p < 0.05$.

0.25 and 1 µmol of pyrilamine caused a greater blockade than 0.05 µmol. The highest dose of pyrilamine (1 µmol) decreased the number of paw elevations by 97.8% when compared to formalin. In the promethazine group, 1 µmol reduced paw elevation by 92%, and 1 µmol of cetirizine decreased it by 23.9%, which was not significant. The intraperitoneal administration of pyrilamine, promethazine, and cetirizine did not reduce the number of elevations (Figure 2A). In phase II, all three drugs in the doses of 0.05, 0.25, and 1 µmol reduced the number of elevations, but the blockade was greater with 0.25 and 1 µmol. In the highest dose, pyrilamine decreased the number of elevations by 93.5%, promethazine reduced by 78.2%, and cetirizine by 80.1%. Significant differences among the drugs were not observed. The intraperitoneal administration of pyrilamine and cetirizine did not change the number of elevations, but promethazine led to a partial reduction (Figure 2B).

In the second part of the study, the drugs were tested for the presence of a clinically evident local anesthetic effect. In phase I, pyrilamine and promethazine decreased the number of paw elevations by 96.7% and 73.3% respectively, and cetirizine decreased by 23.9% which was not significant

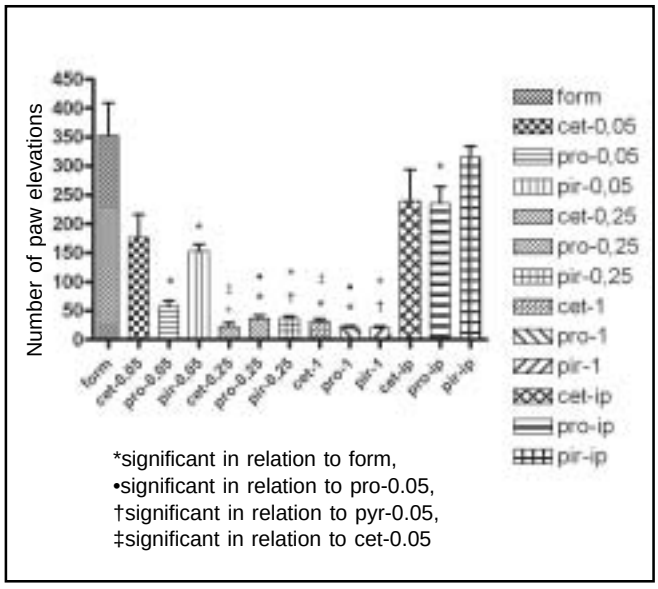


Figure 2B – Effects of the Local or Intraperitoneal Administration of $H_1$ Receptor Antagonists on the Number of Paw Elevations in Phase II. Higher doses (0.25 and 1 µmol) of the three drugs blocked phase II. The intraperitoneal administration of pyrilamine and cetirizine did not block phase II, and promethazine caused a partial blockade. Results shown as mean ± standard error, $p < 0.05$

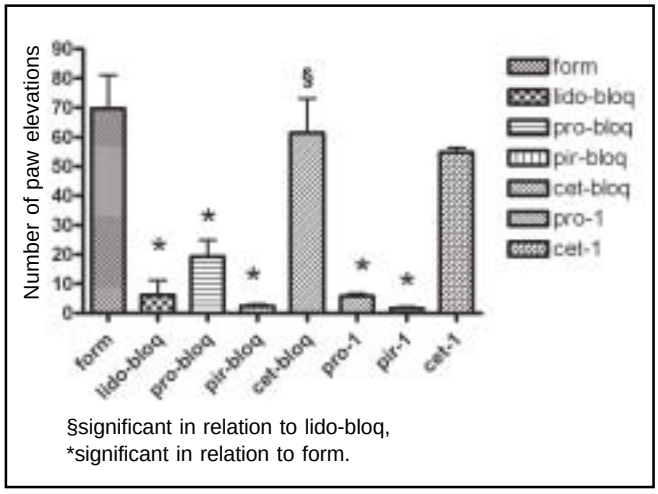


Figure 3A – Number of Paw Elevations After the Local Administration or Peripheral Nerve Block with Pyrilamine, Promethazine, and Cetirizine in Phase I. When used in peripheral nerve block, pyrilamine and promethazine blocked phase I, which was not different from the effects of lidocaine. When compared to lidocaine, cetirizine did not block phase I and showed no difference from formalin. Results shown as mean ± standard error, $p < 0.05$.

when compared to the formalin group (Figure 3A). In phase II, pyrilamine and promethazine decreased the number of paw elevations by 86.6% and 64.4% respectively, while cetirizine decreased it by 19.9% which is not significant when compared to the formalin group (Figure 3B).

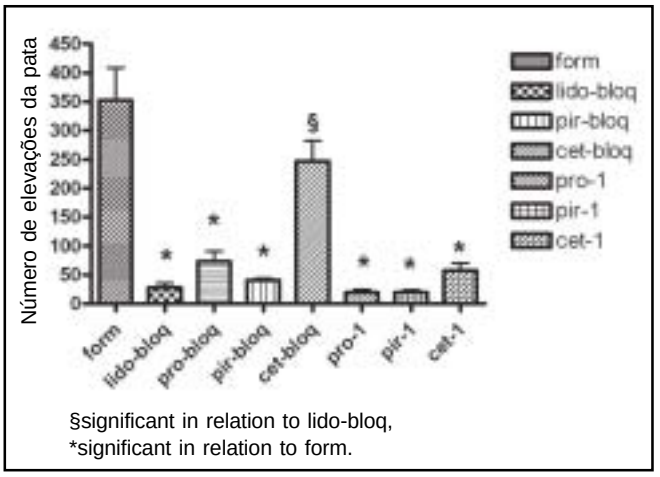


Figure 3B – Number of Paw Elevations in Phase II after Local Administration or Peripheral Nerve Block with Pyrilamine, Promethazine, and Cetirizine. When used in peripheral nerve block, pyrilamine and promethazine blocked phase I, showing no differences when compared to lidocaine. When compared to lidocaine, cetirizine did not block phase II and showed no differences from formalin. Results shown as mean ± standard error, $p < 0.05$.

## DISCUSSION

In the present study the analgesic effects of three $H_1$ receptor antagonists were evaluated in the formalin-induced pain model in rats. The number of paw elevations was used to quantify the painful behavior induced by formalin because it presents an important correlation with the classical formalin test and the cardiovascular changes induced by the response to pain induced by the administration of formalin in the paw. By presenting a reliable correlation with the painful behavior in awake animals not exposed to physical restriction and among the different stereotyped behaviors in the formalin test, the frequency of paw elevations has been widely used [4,15,18-20,22-2].

Most studies on the analgesic effects of histamine receptor antagonists have focused on the central effects [8,12,25-27]. Studies on the peripheral analgesic effects are rare. Two studies explored the analgesic effects of $H_1$ and $H_2$ receptor antagonists, demonstrating important local analgesic effect of pyrilamine and, with lower intensity, cimetidine [14,15]. Pyrilamine blocked both phases of the formalin test, but it was not clear whether the effect observed was class- ($H_1$ receptor antagonist) or pyrilamine-specific.

We tried to clarify this matter by studying three different $H_1$ antagonists: pyrilamine, derived from aminopyridine, promethazine, derived from propilamine, and cetirizine, a newer antagonist derived from piperazine. All three $H_1$ receptor antagonists demonstrated local analgesic effects; however, the action of cetirizine was different from the analgesic actions observed with pyrilamine and promethazine.

The effect observed in the second phase was expected, since this phase of the test is secondary to the local anti-inflammatory effects of formalin [18,28,29]. Histamine is one of the mediators released during inflammation and has pronociceptive effects. The anti-inflammatory action of $H_1$ receptor antagonists was observed with cetirizine, which blocked specifically phase II. The blockade of the first phase shown previously with pyrilamine [14,15] was also seen with promethazine. Those effects were not expected as a result of the action on $H_1$ receptors, since it is believed that phase I results from the direct activation of nociceptors by formalin [30,31]. However, some authors believe that this phase is also inflammatory similarly to phase II [14]. We do not believe that phase I is inflammatory and the fact that cetirizine did not block this phase may be an indication. We believe that the blockade in the first phase after the coadministration of pyrilamine and promethazine with formalin was too fast to be a result of an anti-inflammatory action. In phases I and II, the blockade cannot be attributed to systemic effects, since the intraperitoneal administration of those drugs did not affect the number of paw elevations.

Pyrilamine and promethazine showed analgesic effects similar to those of lidocaine, with analgesia when administered in peripheral nerve block. These data suggest that those $H_1$ receptor antagonists have local anesthetic action, explaining the complete blockade observed in phase I with both drugs. A local anesthetic effect has already been proposed for promethazine [32], but not for pyrilamine.

According to the results of the present study, $H_1$ receptor antagonists showed local anesthetic effect of two natures; an anti-inflammatory effect, which antagonizes peripheral $H_1$ receptors (class-specific), and another similar to the local anesthetic effect, which seems to be drug-specific (pyrilamine and promethazine).

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**RESUMEN:**
Ashmawi HA, Braun LM, Sousa AM, Posso IP - Efecto Analgésico de Antagonistas del Receptor de la Histamina H1 en un Modelo de Dolor Provocado por Formalina en Ratones.

***JUSTIFICATIVA Y OBJETIVOS****: Los receptores de histamina intermedian las vías nociceptivas, principalmente en el sistema nervioso central. Algunos estudios arrojaron un efecto analgésico de antagonistas de receptor de histamina en el sistema nervioso periférico. No queda claro si el efecto analgésico local es de clase específico o un fármaco específico.*

***MÉTODO****: Para responder a esa pregunta, utilizamos tres diferentes antagonistas del receptor H1 (pirilamina, prometazina y cetirizina), administrados directamente en la pata del ratón, por vía intraperitoneal o por bloqueo de nervio periférico en modelo de dolor inducido por formalina. Observamos el efecto de los fármacos en el comportamiento del número de elevaciones de la pata.*

***RESULTADOS****: En la fase I, la pirilamina local redujo el número de elevaciones de la pata de forma dosis dependiente. En la dosis más alta, la reducción fue de un 97,8%. Para la prometazina, la disminución fue de un 92% y para la cetizirina de 23.9%. En la fase II, la pirilamina redujo el número de elevaciones de la pata en un 93,5%, la prometazina, un 78,2% y la cetirizina un 80,1%. La administración de los fármacos por vía intraperitoneal no alteró el comportamiento doloroso. Cuando se usaron para bloqueo del nervio periférico en la fase I, la pirilamina redujo el número de elevaciones de la pata en un 96,7%, la prometazina en un 73,3% y la cetirizina en un 23,9%. En la fase II, la pirilamina redujo un 86,6%, la prometazina un 64,4% y la cetirizina un 19,9%.*

***CONCLUSIONES****: Los resultados mostraron que los antagonistas del receptor de la histamina H1 presentaron efectos analgésicos locales, diferentes del efecto sistémico, siendo uno de ellos antiinflamatorio y clase específico, y el otro específico para la prometazina y la pirilamina, parecido con el efecto clínico anestésico local.*