

JMF2-1, a lidocaine derivative acting on airways spasm and lung allergic inflammation in rats

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Background: Prior reports show that nebulized lidocaine might be an effective treatment for asthma.

Objective: We sought to determine the anti-inflammatory and spasmolytic effects of lidocaine and its analogue, JMF2-1, which we have synthesized for reduced local anesthetic activity. **Methods:** Blockade of Na⁺ currents was assayed in cultured GH₃ cells by using the patch-clamp technique, whereas anesthesia was assessed in a cutaneous pinching test in rats. Lidocaine and its analogue were nebulized into sensitized rats for evaluation of their effectiveness on airways spasm and inflammation induced by methacholine and allergen, respectively. Tissue histamine release and tracheal spasm triggered by allergen challenge in the absence and presence of these treatments were also examined *in vitro*.

Results: The 50% inhibitory concentration values for blockade of Na⁺ currents after treatment with JMF2-1 (25.4 mM) was remarkably higher than that of lidocaine (0.18 mM), which is consistent with the weak anesthetic capacity of this analogue. In contrast, JMF2-1 was more potent than lidocaine in inhibiting allergen-induced histamine release and tracheal spasm. In *in vivo* settings methacholine-induced increase in lung resistance (145%) significantly reduced to 72% and 47% after lidocaine and JMF2-1 treatment, respectively. Both treatments

inhibited by about 81% allergen-evoked eosinophil accumulation into the lung tissue.

Conclusion: Replacement of the 2,6-dimethyl radicals by the 2-trifluoromethyl group on the benzene ring of lidocaine significantly reduces anesthetic activity, preserving its ability to prevent key aspects of the allergic inflammatory response in the lung.

Clinical implications: Nebulized JMF2-1 might be a means of achieving the antiasthmatic effects of lidocaine without the anesthetic effects. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, local anesthetics, lidocaine, rat model

Asthma is defined as a chronic inflammation of the lung airways caused by environmental factors in genetically predisposed individuals. Episodic airway obstruction and bronchial hyperresponsiveness to nonspecific irritants are the major symptoms of this disease, which is on the increase in many countries and can be fatal.^{1,2} Inflammation is central in the pathogenesis of asthma. The antigens activate mast cells and T_H2 lymphocytes in the airways, which then release preformed and neosynthesized inflammatory mediators, including vasoactive amines, lipid mediators, and cytokines, such as IL-4, IL-5, and IL-13.^{1,3} A marked feature of this process is the massive infiltration of eosinophils. Interestingly, numerous experimental and clinical observations have linked eosinophil derivatives with the asthmatic dysfunction, leading to the assumption that drugs able to downregulate eosinophil recruitment and activation might have great therapeutic potential in asthma control.¹⁻³

Local anesthetics are known for their ability to block voltage-sensitive sodium channels, which are responsible for the increase in sodium permeability during the rapid rising phase of the action potential in excitable cells, such as neurons and cardiac and smooth muscle cells.⁴ Lidocaine, first synthesized in 1943, is still largely used as a short-acting local anesthetic and antiarrhythmic agent. However, it is now well established that lidocaine has also significant effects on nonexcitable cells, including neutrophils,⁵ monocytes,⁶ T_H2 lymphocytes,⁷ mast cells,⁸

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Abbreviations used

IC₅₀: 50% inhibitory concentration
 Pes: Esophageal pressure
 Ptr: Tracheal pressure
 V': Airflow

and eosinophils,⁹⁻¹¹ raising the possibility of alternative clinical uses to control chronic inflammatory diseases, including asthma.

In 1996, Ohnishi et al¹¹ first reported the proapoptotic effect of lidocaine on eosinophils *in vitro*, strongly motivating further studies in asthmatic patients. In fact, recent clinical observations support the interpretation that lidocaine has glucocorticoid-sparing properties in atopic asthmatic subjects, as attested by a significant increase in FEV₁ measurements and reduction in nighttime awakenings, symptoms, bronchodilator use, and blood eosinophil counts.¹²⁻¹⁵

It is well established that in asthmatic patients airway instrumentation, such as endotracheal intubations, can cause life-threatening bronchospasm¹⁶ and that lidocaine, when administered both intravenously or as an aerosol, significantly attenuates that sort of reflex bronchoconstriction.¹⁷ Inhaled lidocaine can also diminish the response to an inhalational provocation with hyperosmolar saline solution,¹⁸ histamine,¹⁹ and water.²⁰ On the other hand, the usefulness of this treatment in asthma is still debatable because lidocaine itself produces an initial airway irritation and bronchoconstriction in asthmatic patients, as attested by a reduction in FEV₁ and other changes.²¹⁻²⁵ While trying to gain further understanding of the mechanism of action of local anesthetics in asthma, we sought to compare the putative anti-inflammatory and spasmolytic effects of lidocaine with those of a structural lidocaine analogue, 2-diethylamine-2'-trifluoromethyl-acetoanilide hydrochloride, here termed JMF2-1, which we have synthesized and screened for reduced local anesthetic activity.

METHODS

Animals

Wistar rats (180-250 g) and Swiss-Webster mice (20-25 g) were obtained from the Oswaldo Cruz Foundation breeding facility and kept in the animal-housing facilities of the Department of Physiology and Pharmacodynamics at a controlled room temperature (22°C-25°C) and with a 12-hour (6 AM-6 PM) light/dark cycle. All the procedures involving care and use of laboratory animals in this study were examined and approved by the Animal Ethics Committee of the Oswaldo Cruz Foundation (CEUA-FIOCRUZ, Prot. 00085-02).

Neurobehavioral evaluation

The nocifensive cutaneous reaction was evaluated in naive rats on the basis of the withdrawal reflex to pinching on cutaneous sites on their backs that were previously injected intradermally with increasing doses of lidocaine or analogues (1-4 μ mol per site) in a final volume of 50 μ L in 5-minute intervals. An area of anesthesia was considered present when the rat did not squeak or withdraw the skin within 4 seconds of starting skin clamping, as previously described.²⁶

Lidocaine and JMF2-1 solutions were prepared by using physiologic saline (0.9% NaCl solution).

Whole-cell voltage clamp experiments, cell culture, and treatments

Rat clonal pituitary GH₃ cells were kindly provided by Eduardo Arzt (Laboratory of Physiology and Molecular Biology, University of Buenos Aires, Buenos Aires, Argentina). GH₃ cells were cultured in RPMI 1640 medium containing 10% FCS, penicillin (100 U/mL), and streptomycin (100 μ g/mL) and plated on a glass sheet at 37°C in a 5% CO₂ humidified atmosphere to be used within 1 to 2 days. Ion-channel currents in GH₃ cells were recorded by means of a patch-clamp technique.²⁷ Na⁺ currents were recorded in saline solution in the presence or absence of lidocaine or JMF2-1.

Anaphylactic histamine release from rat subcutaneous tissue fragments *in vitro*

Immunized rats were killed in a CO₂ atmosphere, and fragments from dorsal subcutaneous tissue (approximately 1 mg) were removed and placed in 48-well plates containing HBSS with Ca⁺⁺ and Mg⁺⁺ in a final volume of 700 μ L. The fragments were exposed to ovalbumin (300 μ g/mL) for 1 hour, and then the plates were centrifuged at 150g for 10 minutes, and the samples were collected and added to 0.8 N perchloric acid (1:2 dilution) as previously reported.²⁸ The tissue system was pretreated with the target substance or its vehicle at 37°C for 1 hour to test the potential effect of lidocaine and JMF2-1 (10⁻⁹ to 10⁻³ M) on ovalbumin-evoked histamine release. After centrifugation at 170g for 10 minutes, the supernatant was collected and stored at -20°C for histamine fluorimetric quantification, as previously reported.²⁹

For laboratory procedures concerning (1) isolated tracheal preparation and measurement of tension, (2) assessment of *in vivo* respiratory mechanics, and (3) sensitization, challenge, and treatments, see the Methods section in the Online Repository at www.jacionline.org.

Seizure incidence

Mice were randomly divided into groups of 10 animals. Ten minutes after intraperitoneal administration of lidocaine or JMF2-1 (40-500 mg/kg), the animals were observed for the occurrence or absence of seizures, as previously reported.³⁰

Chemicals

Lidocaine hydrochloride was donated by Nortec Química Desenvolvimento Tecnológicos S.A. (Duque de Caxias, RJ, Brazil). JMF2-1.HCl was synthesized from 2-trifluoromethyl-aniline in the Department of Organic Synthesis of Farmanguinhos (FIOCRUZ, Rio de Janeiro, Brazil). Albuterol sulfate was donated by GlaxoSmithkline (Rio de Janeiro, Brazil). Lidocaine, JMF2-1, and albuterol were dissolved in saline solution immediately before use.

Statistical analysis

Statistical analysis involving 2 groups was done with the Student *t* test, whereas ANOVA and the Newman-Keuls-Student test were used to compare more than 2 groups. *P* values of .05 or less (2-tailed test) were considered significant.

RESULTS

Duration of anesthesia after intradermal application of lidocaine and JMF2-1 in rats

The nocifensive reaction was evaluated in naive rats by means of the withdrawal reflex to pinching on cutaneous

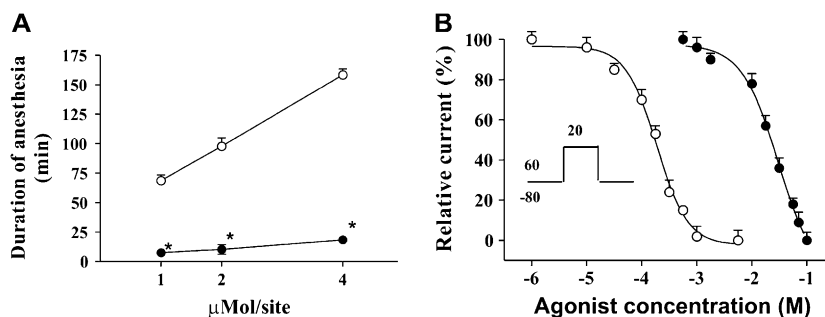


FIG 1. Local anesthesia activity and whole-cell recording of Na⁺ channel currents. **A**, Duration to full recovery of sensory block (mean $\pm$ SD, $n = 6$) after intradermal injection of increasing doses of lidocaine (open circles) and JMF2-1 (solid circles) in rats. * $P < .05$ compared with lidocaine-treated group. **B**, Tonic block of Na⁺ currents in GH₃ cells by lidocaine (open circles) and JMF2-1 (solid circles). Data are reported as the means $\pm$ SD ($n = 6$ for all groups, with at least 3 independent experiments).

sites previously injected with increasing doses of lidocaine or JMF2-1 (1–4 μ mol per site). As shown in Fig 1, A, our findings indicated that the duration of complete blockade for the nocifensive response was clearly longer with lidocaine in doses ranging from 1 to 4 μ mol per site.

Blockade of Na⁺ channels with lidocaine and JMF2-1

Because JMF2-1 presented reduced local anesthetic activity compared with lidocaine, we wanted to compare the effectiveness of these molecules on Na⁺ current blockade by means of patch-clamp recording of GH₃ cells. Voltage-gated Na⁺ currents were recorded from these cells in the presence or absence of either lidocaine or JMF2-1. In control experiments ($n = 6$) GH₃ cells were depolarized from a holding potential -80 mV to $+60$ mV step pulse (2-second duration), leading to inward Na⁺ currents (data not shown). In addition, bath application of increasing tetrodotoxin concentrations inhibited Na⁺ channel currents with a 50% inhibitory concentration (IC₅₀) of 304 nmol/L (curve concentration-response not shown), confirming the presence of tetrodotoxin-sensitive voltage-gated Na⁺ channels in GH₃ cells. Marked blockade of Na⁺ currents was also noted after treatment with increasing concentrations of lidocaine (IC₅₀, 0.18 mmol/L), as expected (Fig 1, B). Remarkably, treatment with JMF2-1 (Fig 1, B) inhibited Na⁺ currents in GH₃ cells, but the concentrations required were significantly higher. In fact, the IC₅₀ of JMF2-1 (25.4 mmol/L) was found to be 169 times higher than that noted in the case of lidocaine.

Effect of lidocaine and JMF2-1 on allergen-evoked histamine release

Using a model of anaphylactic histamine release from rat subcutaneous tissue fragments *in vitro*, we compared the putative mast cell-stabilizing properties of lidocaine and JMF2-1. As shown in Fig 2, lidocaine inhibited the allergen-evoked histamine release, and so did JMF2-1, but the latter was shown to be about 28 times more potent than the former (IC₅₀, 4.5 and 0.16 μ mol/L, respectively).

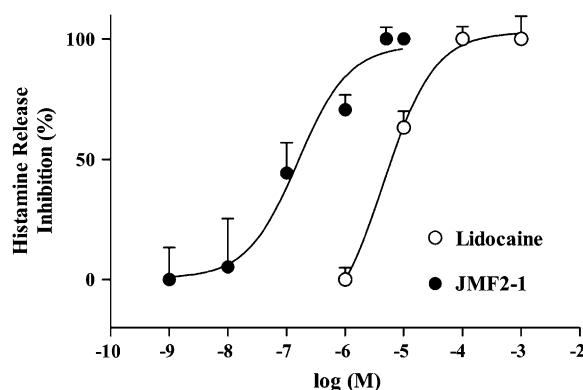


FIG 2. Histamine release inhibition. Blockade of allergen-evoked tissue histamine release caused by treatment with increasing concentrations of either lidocaine (open circles) or JMF2-1 (solid circles). Values are expressed as means $\pm$ SD from at least 4 experiments.

Effect of lidocaine and JMF2-1 on the anaphylactic tracheal spasm

In a set of *ex vivo* experiments, we investigated the effect of lidocaine and JMF2-1 on allergen-evoked tracheal spasm. Contractions were induced by ovalbumin (100 μ g/mL) in isolated trachea obtained from actively sensitized rats. As shown in Fig 3, lidocaine (Fig 3, A) and JMF2-1 (0.3–3 mM; Fig 3, B) inhibited ovalbumin-evoked contraction in a concentration-dependent manner. Compared with lidocaine, the efficacy of blockade appeared significantly higher in the JMF2-1-treated condition. Pretreatment with albuterol (0.045, 0.136, and 1 mM) also inhibited anaphylactic tracheal spasm in a concentration-dependent manner, as expected (Fig 3, C).

Effect of lidocaine and JMF2-1 on the [Ca²⁺]_i-tension relationship

Because lidocaine directly relaxes airway smooth muscle by decreasing both Ca²⁺ influx and mobilization of stored Ca²⁺,³¹ we further compared the effects of lidocaine and JMF2-1 on tracheal contraction induced by

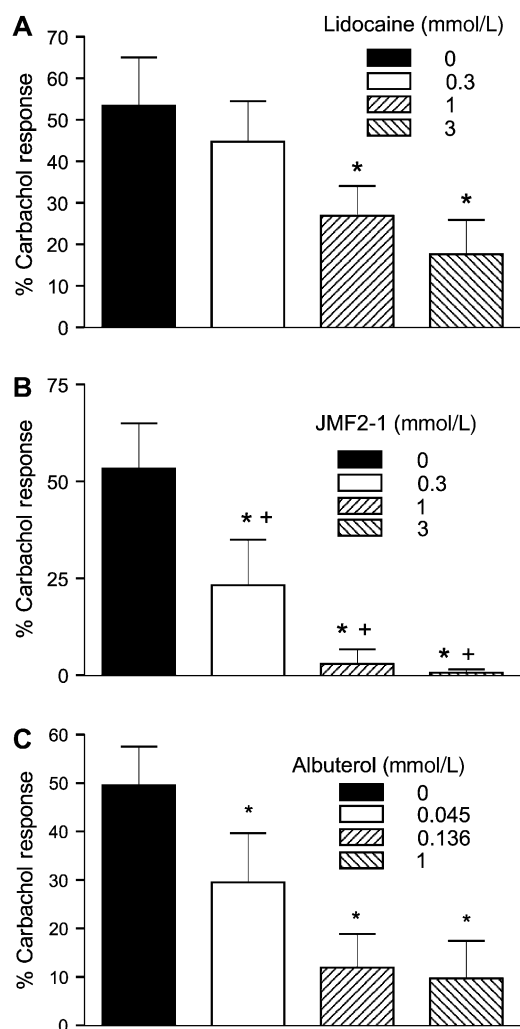


FIG 3. *Ex vivo* tracheal spasm blockade. Inhibitory effect of lidocaine (A), JMF2-1 (B), and albuterol (C) on the anaphylactic contraction evoked by ovalbumin (100 μ g/mL) in rat tracheas. Values are expressed as means $\pm$ SD from at least 6 experiments. * P < .05 compared with the untreated group; + P < .05 compared with the lidocaine-treated group.

changes in extracellular Ca^{2+} concentrations during high K^{+} depolarization. Fig 4 shows that in response to a step-wise increment in extracellular Ca^{2+} concentration, tracheal contraction increased in a concentration-dependent manner in a mechanism sensitive to JMF2-1 (0.1 and 1 mmol/L; Fig 4, A). Lidocaine also prevented the phenomenon, but the blockade was apparent only at the higher concentration (1 mmol/L; Fig 4, B).

Effects of lidocaine and JMF2-1 on methacholine-evoked airways spasm

In naive rats treated intravenously with either lidocaine or JMF2-1 (1 mg/kg), we found a marked attenuation in the increase in lung resistance induced by 100 μ g/kg methacholine injected intravenously. Values in percentages of increase from baseline after intravenous injection of methacholine measured within 3 minutes of

provocation reduced from $145\% \pm 35\%$ in saline-treated animals to $72\% \pm 6\%$ and $47\% \pm 18\%$ after lidocaine and JMF2-1 (P < .05 compared with untreated rats), respectively. In contrast, both treatments failed to alter methacholine-evoked increases in dynamic elastance (see Table E1 in the Online Repository at www.jacionline.org).

Effects of nebulized lidocaine and JMF2-1 on allergen-evoked cell influx into the lung

Actively sensitized rats were aerosolized with 5% ovalbumin for 30 minutes separately or in combination with either lidocaine or JMF2-1 at 5% to study the effect of lidocaine and JMF2-1 on allergen-evoked lung inflammation. Treatment, but not provocation, was repeated once more within 8 hours. The scheme of provocation and treatment was repeated the day after, and the cellular analysis was performed in lung tissue digest samples obtained 48 hours after the first provocation. As shown in Fig 5, compared with sham-challenged control animals, allergen stimulation caused a marked increase in total leukocyte numbers (Fig 5, A), which was accounted for by an increase in the number of mononuclear cells (Fig 5, B), eosinophils (Fig 5, C), and neutrophils (Fig 5, D). All these changes, except augmentation in mononuclear cell counts, were sensitive to treatment with either lidocaine or JMF2-1.

Proconvulsive effect of lidocaine and JMF2-1

In an attempt to assess the neurotoxic profile of JMF2-1 in comparison with that of lidocaine, we evaluated the convulsive effect of these molecules in mice. Increasing doses of each compound were intraperitoneally injected into distinct groups of 10 animals, and the incidence of convulsion was determined. The dose of lidocaine necessary to cause convulsion in 50% of the animals (63 mg/kg) was 4.3-fold lower than the dose of JMF2-1 (273 mg/kg). Moreover, 10 of 10 animals tested had convulsion at a concentration of 80 mg/kg lidocaine. Of note, it was not possible to cause convulsive events in mice with doses equal or lower than 200 mg/kg after JMF2-1 treatment (see Fig E1 in the Online Repository at www.jacionline.org).

DISCUSSION

Local anesthetics, particularly lidocaine, are arousing interest as possible new pharmacologic agents for the treatment of asthma.¹²⁻¹⁵ Nevertheless, topical anesthesia of the airways has been associated with discomfort and side effects. The present study investigated the possibility that nonanesthetic lidocaine derivatives might preserve the anti-inflammatory and spasmolytic activities of the parent compound. We reported here that the lidocaine analogue JMF2-1, which we synthesized and screened for reduced local anesthetic activity, was able to prevent both methacholine-evoked airways spasm in naive rats and allergen-evoked neutrophil and eosinophil infiltration into the lungs of actively sensitized rats. It also inhibited histamine release *in vitro*, as well as allergen-evoked tracheal contraction in *ex vivo* settings, and evidence suggests

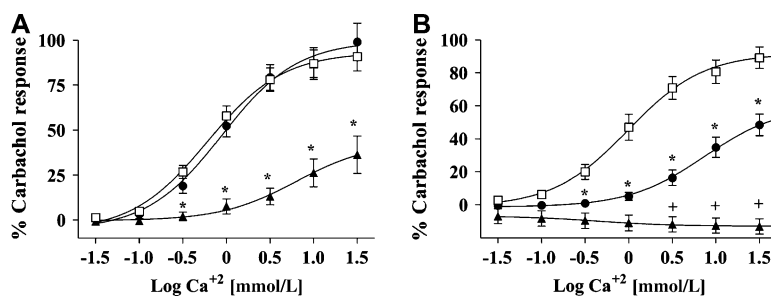


FIG 4. Interference on the Ca^{2+} -tension relationship. Effect of lidocaine (**A**) and JMF2-1 (**B**) at concentrations of zero (squares), 0.1 mM (circles), and 1 mM (triangles) on the contraction development induced by changes in extracellular Ca^{2+} during 100 mM K^{+} depolarization. Values are expressed as means $\pm$ SEM from at least 4 experiments. * $P < .05$ compared with the untreated group; + $P < .05$ compared with the 0.1 mM JMF2-1-treated group.

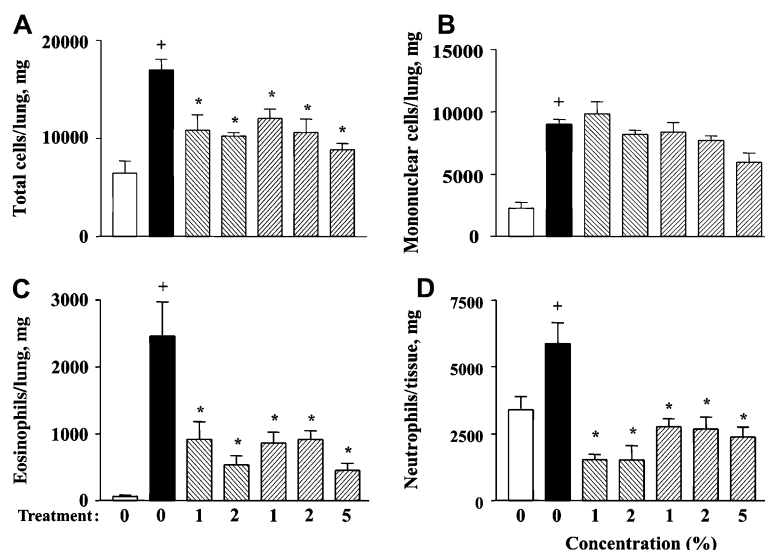


FIG 5. Lung tissue leukocytes. Effect of lidocaine (left-hatched columns) and JMF2-1 (right-hatched columns) on total leukocytes (**A**), mononuclear cells (**B**), eosinophils (**C**), and neutrophils (**D**) infiltrated in the lung tissue of sensitized and ovalbumin-challenged rats. Values are expressed as means $\pm$ SEM from at least 6 animals. + $P < .05$ compared with the sensitized, saline-challenged group (open columns); * $P < .05$ compared with the ovalbumin-challenged and saline-treated group (closed columns).

that the spasmolytic effect is at least in part accounted for by blockade of Ca^{2+} influx. These findings support the interpretation that JMF2-1 might have clinical value as a therapeutic alternative for asthma control, with advantages over local anesthetics.

Lidocaine's aromatic tail is a major structural feature that determines the interaction of local anesthetics with voltage-operated Na^{+} channels, causing their reversible blockade.³² Our findings revealed that the potency in blocking voltage-operated Na^{+} channels in GH₃ cells of JMF2-1, a lidocaine analogue resulting from structural changes in the aromatic tail, was markedly reduced compared with the potency of the parent compound lidocaine. In fact, the IC_{50} value for blockade of Na^{+} currents by JMF2-1 was 169-fold higher than the lidocaine IC_{50} value. In parallel, we found about 90% reduction in the duration of JMF2-1 anesthetic activity, according to the cutaneous pinching test. This difference was not as great as would be predicted from the results concerning Na^{+} current

blockade by these molecules, which might be accounted for by pharmacokinetic reasons.

It is well established that local anesthetics have pharmacologic properties beyond local anesthesia, most of them resulting from their interaction with other cellular systems than excitable cells.³³ For instance, the function of mast cells and basophils, which are histamine-storing cells deeply implicated in allergic dysfunctions, is markedly sensitive to local anesthetics; both IgE-dependent and IgE-independent histamine release are blocked by lidocaine treatment in a mechanism involving a decrease in calcium influx.³⁴⁻³⁶ Using a model of allergen-evoked histamine release *in vitro*, we found strong evidence that the anti-inflammatory effect of lidocaine could be dissociated from its ability to block Na^{+} currents and cause local anesthesia. In fact, we found that in spite of being about 2 orders of magnitude less active than lidocaine in terms of blockade of Na^{+} channels, JMF2-1 was 30-fold more potent than the local anesthetic concerning blockade of

histamine release, confirming the hypothesis that a non-anesthetic lidocaine analogue might have improved the ability to prevent allergic inflammation exhibited by the parent compound.

Several studies have demonstrated that lidocaine directly relaxes airway smooth muscle^{31,35,37} and can prevent life-threatening bronchospasm in human subjects.^{17,18,20} While trying to compare the effects of lidocaine, JMF2-1, and albuterol on allergen-evoked rat tracheal spasm, we noted that both lidocaine and albuterol did not modify the basal tonus but caused a concentration-dependent blockade of tracheal anaphylactic contraction. These findings are in line with prior publications in which the antispasmodic effect of lidocaine was reported.³⁵ JMF2-1 also did not alter tracheal baseline tonus and was significantly more effective than lidocaine in inhibiting allergen-evoked tracheal contraction in all concentrations tested, which might be at least in part related to its higher potency in preventing allergen-evoked histamine release.

Recent clinical investigations have shown the efficacy of nebulized lidocaine in the treatment of asthmatic patients.¹²⁻¹⁵ The interest in local anesthetics as alternative agents for the treatment of asthma has been strongly motivated by the findings that eosinophil survival and activation are highly sensitive to lidocaine *in vitro*.⁹⁻¹¹ Although treatment of asthmatic patients has clearly revealed a reduction in the number of blood eosinophils and asthma symptoms in parallel with an increase in FEV₁ measurements, no data are available in the literature concerning the putative influence of lidocaine on lung eosinophil numbers, either in patients or experimental animals. While trying to clarify the effects of local anesthetics in the airways subjected to allergic inflammation, we showed that treatment of actively sensitized rats with aerosols of lidocaine or JMF2-1 equally prevented the lung eosinophilic infiltration triggered by allergen challenge. Remarkably, these treatments also inhibited neutrophil, but not mononuclear cell, accumulation into the lung tissue. Because mononuclear cell counts embrace both macrophages and lymphocytes, further studies are now underway to clarify the sensitivity of each one of these leukocyte subtypes. It is noteworthy that the inhibitory effect of lidocaine on T cells from asthmatic subjects has been reported,⁷ raising the possibility that a blockade of CD4⁺ T-cell proliferation, T_H2 cytokine generation, or both could be underlying the anti-inflammatory action of lidocaine and JMF2-1. The ability of lidocaine to down-regulate eosinophil activation and survival,⁹⁻¹¹ mast cell degranulation,^{8,36} or both might also contribute to this suppressive mechanism.

Throughout the literature, there are conflicting reports concerning the putative benefits of nebulized lidocaine on bronchoconstriction induced by histamine, hyperosmolar saline, and exercise in asthmatic patients.^{13,14,24,38-40} Our findings revealed that airways constriction induced by intravenous injection of methacholine in rats was markedly attenuated by both lidocaine and JMF2-1. On the contrary, both treatments failed to alter the methacholine-evoked increase in lung dynamic elastance. These results, in combination with those in which lidocaine's capacity to prevent

allergen-induced lung recruitment of inflammatory cells is demonstrated, might help to explain the therapeutic benefits devoted to this local anesthetic in studies involving asthmatic patients.^{13,14} On the other hand, our findings are consistent with the interpretation that JMF2-1 does have relevant anti-inflammatory and spasmolytic properties *in vivo* and can therefore relieve breathlessness and exert antiasthma actions without inducing the long-lasting topical anesthesia of lidocaine. Of note, in a comparative analysis involving inhalation of distinct local anesthetics by volunteers with bronchial hyperreactivity, the longest-lasting and most intense anesthesia brought about by dyclonine inhalation was not enough to prevent airways hyperreactivity noted after histamine challenge under conditions in which both lidocaine and ropivacaine significantly attenuated the phenomenon.³⁸ Evidence from the literature indicates that substances acting on Na⁺ channels, such as local anesthetics, including lidocaine, could also block the function of Ca²⁺ channels.³¹ Evidence from our *ex vivo* experiments also gives support to this interpretation, pointing out that JMF2-1 was clearly more potent than lidocaine in inhibiting the extracellularly applied Ca²⁺-induced tracheal tension during high K⁺ depolarization, probably by inhibiting influx of Ca²⁺ into the smooth muscle cells. Altogether, these results reinforce the potential usefulness of this nonanesthetic lidocaine derivative in controlling allergic dysfunctions, leading to the assumption that JMF2-1 might indeed serve as an innovative prototype in drug discovery for asthma syndromes.

Finally, it should be emphasized that the toxicity of local anesthetics, including lidocaine, is closely related to the potency of the local anesthetic because toxicity is largely dependent on the blockade of Na⁺ channels within the central nervous system and cardiovascular system.⁴ In fact, our findings indicated that the proconvulsive potency of lidocaine was significantly higher than that presented by JMF2-1, as expected by the short-lasting and weak anesthesia developed by this analogue, suggesting that JMF2-1 might prove to be safer than lidocaine for patients with asthma. However, because, unlike lidocaine, JMF2-1 is halogenated with a trifluoromethyl substitution at the benzene ring, experiments should be done to better define the safety profile of this substance, mainly concerning hepatic injury.

In conclusion, these observations suggest that the anesthetic action might not be relevant in the anti-inflammatory and spasmolytic activity of local anesthetics and provide support for the belief that the lidocaine derivative JMF2-1, when inhaled, might achieve useful clinical benefit for the treatment of asthma.

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