

Serra MF, Neves JS, Couto GC, Cotias AC, Pão CR, Olsen PC, de Carvalho KI, Anjos-Valotta EA, Faria RX, Costa JC, Cordeiro RS, Silva PM, Martins MA. (2016). JM25-1, a lidocaine analogue combining airway relaxant and anti-inflammatory properties: implications for new bronchospasm therapy. *Anesthesiology* 124(1):109-20.

BACKGROUND:

Inhaled lidocaine antagonized bronchospasm in animal models and patients, but adverse effects limited its efficacy. This study evaluated the antibronchospasm potential of the analog JM25-1, exploring in vitro mechanisms and translation to an animal model.

METHODS:

The effectiveness of JM25-1 was assessed in GH3 cells, rat tracheal rings, mouse lymphocytes, and human eosinophil systems in vitro, assessing changes in Na current, contraction, proliferation, and survival, respectively. Lung function and inflammatory changes were studied in ovalbumin-sensitized mice.

RESULTS:

The efficacy of JM25-1 was higher than lidocaine in inhibiting carbachol-induced and calcium-induced tracheal contractions (maximum effect inhibition at 1 mM [%]: 67 ± 10 [JM25-1] vs. 41 ± 11 [lidocaine] [$P < 0.001$] for carbachol; 100 ± 3 [JM25-1] vs. 36 ± 26 [lidocaine] [$P < 0.001$] for Ca; mean \pm SD; n = 9 each) but lower in Na current (50% inhibitory concentration = 151.5, n = 8 vs. 0.2 mM; n = 5; $P < 0.001$). JM25-1 also inhibited eosinophil survival (dead cells [%]: 65 ± 6 ; n = 4; $P < 0.001$ at 1 mM) and lymphocyte proliferation (cells in phase S + G2 [%]: 94 ± 10 ; n = 6; $P < 0.001$) at 0.6 mM. Aerosolized JM25-1 (1%) decreased lung eosinophil numbers from 13.2 ± 2.4 to $1.7 \pm 0.7 \times 10/\mu\text{m}$ (n = 6; $P < 0.001$) and neutrophils from 1.9 ± 0.4 to $0.2 \pm 0.1 \times 10/\mu\text{m}$ (n = 7; $P < 0.001$). Other parameters, including airway hyperreactivity, cytokines, mucus, and extracellular matrix deposition, were also sensitive to aerosolized JM25-1.

CONCLUSION:

These findings highlight the potential of JM25-1, emphasizing its putative value in drug development for clinical conditions where there is bronchospasm.