



Opinion

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The Paradox of Micro-Dosed Salicylates: A Critical Appraisal of Recent Contradictions in Otolaryngological and Respiratory Pharmacology

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Abstract

Aspirin (acetylsalicylic acid) remains a pharmacological mainstay, yet its adverse effects within otolaryngology and pulmonology, specifically salicylate-induced ototoxicity, tinnitus, and Aspirin-Exacerbated Respiratory Disease (AERD), are well-documented. Recent publications by Pugach and Sadeghi-Latefi have introduced a controversial paradigm, suggesting that ultra-low-dose topical aspirin acts as a respiratory-protective anti-inflammatory, while standard systemic doses paradoxically act as pro-inflammatory irritants. This opinion piece critically evaluates these claims, highlighting severe methodological flaws, placebo discrepancies, and internal data contradictions that undermine the proposed paradigm shift.

Keywords: Aspirin; Salicylates; Tinnitus; Aspirin-exacerbated respiratory disease; Pharyngitis; Samter's triad, Arachidonic acid cascade; Therapeutic window; Prostaglandin E2; 5-lipoxygenase pathway

Abbreviations: Cyclooxygenase (COX); Outer hair cells (OHCs); N-methyl-D-aspartate (NMDA) Aspirin Exacerbated Respiratory Disease (AERD); Prostaglandin E2 (PGE2); 5-lipoxygenase pathway (5-LOX); Cysteinyl Leukotrienes (LTC, LTD, LTE); Mucosal Immune Complex (MIC); Nonsteroidal Anti-inflammatory Drugs (NSAIDs); Interleukin 8 (IL8)

Introduction

In the fields of otolaryngology and respiratory medicine, aspirin presents a clinical paradox. While recognized for its potent analgesic and antipyretic properties via irreversible cyclooxygenase (COX) inhibition, its localized and systemic adverse effects are insidious.

Within the auditory system, salicylates rapidly enter the perilymph, competitively binding to the prestin protein in outer hair cells (OHCs) [1]. This alters electromotility and disrupts

the cochlear amplifier, concurrently triggering excitotoxicity in the auditory nerve via N-methyl-D-aspartate (NMDA) receptor overactivation. Clinically, this manifests as reversible sensorineural hearing loss and high-pitched tinnitus.

In the respiratory tract, aspirin is the primary trigger for Aspirin-Exacerbated Respiratory Disease (AERD). By irreversibly inhibiting COX-1, aspirin depletes the respiratory mucosa of Prostaglandin E2

(PGE2), removing the critical “brake” on mast cell degranulation [2]. Consequently, arachidonic acid is aggressively shunted down the 5-lipoxygenase (5-LOX) pathway, resulting in a massive overproduction of cysteinyl leukotrienes (LTC4, LTD4, LTE4). This pathway shift triggers the hallmark bronchoconstriction, nasal polyposis, and severe mucosal edema seen in AERD patients.

Discussion

Against this established backdrop, recent work by Pugach and Sadeghi-Latefi proposes a radical departure from traditional nonsteroidal anti-inflammatory drugs (NSAID) pharmacodynamics [3, 4]. Utilizing a proprietary “Mucosal Immune Complex” (MIC) throat spray, the authors claim that an ultra-low, 6 mg topical dose of aspirin effectively reduces localized respiratory inflammation.

More controversially, they hypothesize a strict “therapeutic window” [3]. They assert that while 6 mg suppresses inflammatory cytokines like PGE2 and Interleukin-8 (IL-8), standard therapeutic doses (e.g., 325 mg) paradoxically increase these cytokines, acting as pro-inflammatory irritants that damage the respiratory epithelial barrier. Based on this, they advocate for micro-dosed topical salicylates as a safe, targeted therapy for common cold symptoms like pharyngitis, allegedly bypassing the toxicity of systemic NSAIDs.

Methodological Flaws

A rigorous critical appraisal of their 2024 randomized controlled trial reveals severe methodological deficiencies that compromise these conclusions, most notably regarding the formulation of the placebo [4].

To establish the efficacy of the 6 mg aspirin dose, it must be isolated against an inert control. However, the active treatment arms in this trial were formulated with a highly active biological matrix (the MIC) containing 0.5% bovine lactoferrin, 5% lysozyme, and 0.2% whole leaf aloe vera juice. Furthermore, the active sprays contained a therapeutic dose of 0.5% menthol.

The placebo arm, by contrast, lacked the aloe, lysozyme, and lactoferrin entirely, and contained only a so-called sub-therapeutic 0.0009% menthol.

By comparing an active spray packed with established antimicrobial agents, soothing mucosal-coating aloe, and highly sensory, analgesic menthol against essentially unflavored water, the trial introduced insurmountable confounding variables. The reported 75% reduction in sore throat pain cannot be scientifically attributed to the 6 mg of aspirin. Furthermore, the stark sensory differences between the therapeutic menthol formulation and the inert placebo effectively unblinded the study, inviting massive psychosomatic and sensory bias.

The Group IV Paradox

Perhaps the most glaring issue within the 2024 trial is how the authors' own clinical data directly refutes their foundational hypothesis [4].

If, as the authors claim, standard systemic doses of aspirin, such as 325 mg, are highly pro-inflammatory and detrimental to the

respiratory barrier, introducing such a dose should theoretically worsen clinical outcomes. Yet, the trial included a fourth treatment arm (Group IV) that administered a mucosal spray alongside a standard 325 mg oral aspirin tablet every four hours.

The results demonstrated that Group IV achieved the highest efficacy across all measured endpoints. It provided the greatest reduction in sore throat pain (79% vs. 75% for topical alone) and nearly double the reduction in overall cold severity as measured by the Modified Jackson Score (69% reduction vs. 38% for topical alone).

The clinical superiority of the systemic 325 mg dose fundamentally dismantles the authors' assertion that high-dose aspirin exacerbates respiratory cold symptoms. Instead, the data simply reaffirms standard pharmacological consensus: a traditional, systemic dose of a COX inhibitor provides superior, predictable anti-inflammatory and analgesic relief compared to an isolated micro-dose.

Conclusion

While exploring highly localized drug delivery systems is a valid and necessary frontier in otolaryngology, the claims presented by Pugach and Sadeghi-Latefi must be viewed with intense skepticism. The assertion that aspirin operates on an inverted, pro-inflammatory dose-response curve in the respiratory tract is not supported by their own *in vivo* clinical data.

Furthermore, the lack of transparency regarding the confounding biological and sensory ingredients in their active formulations versus their placebo invalidates the high efficacy rates reported. Given the known, severe adverse effects of salicylates on the auditory and respiratory systems, promoting a new paradigm of localized safety requires flawless, independently replicated methodology. Until properly blinded trials utilizing identical, isolated placebo matrices are conducted, standard pharmacological principles regarding aspirin's dose-dependent efficacy and toxicity must remain the clinical standard.

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Conflicts of Interest

No conflicts of interest.

References

1. Cazals Y (2000) Auditory sensori-neural alterations induced by salicylate. *Prog Neurobiol* 62(6): 583-631.
2. Kowalski ML, Makowska JS, Blanca M, et al. (2019) Aspirin-exacerbated respiratory disease (AERD): Current understanding of pathogenesis and management. *Immunol Allergy Clin North Am* 39(1): 1-13.
3. Leyva-Grado V, Pugach P, Sadeghi-Latefi N (2021) A novel anti-inflammatory treatment for bradykinin-induced sore throat or pharyngitis. *Immun Inflamm Dis* 9(4): 1199-1210.
4. Pugach P, Sadeghi-Latefi N (2024) Supporting respiratory epithelia and lowering inflammation to effectively treat common cold symptoms: A randomized controlled trial. *PLoS One* 19(1): e0292550.