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BENZYDAMINE
Oropharyngeal formulations
Benzydamine is an anti-inflammatory agent with local anaesthetic and analgesic properties. It was synthesized in the Laboratories of the Angelini Research Institute in the 1960s, and marketed in Italy in the 1970s. It was later released on the market in more than 70 European, American and Asian Countries.

Pharmacodynamic investigations have shown that benzydamine acts as a suppressor of proinflammatory cytokines, especially against Tumor Necrosis Factor-α (TNF-α) and to a lesser extent, Interleukin-1β (IL-1β) and Chemokine ligand 2 (CCL2) monocyte chemotactic protein-1 (MCP-1), that are well known to be potent mediators of inflammation. However, it did not affect other inflammatory cytokines like Interleukin-6 (IL-6) and Interleukin-8 (IL-8) and, importantly, cytokines with anti-inflammatory properties, such as Interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra).

The mechanism of action of benzydamine differs from that of the aspirin-like drugs. The main difference is that benzydamine is - in comparison to aspirin like drugs - a weak inhibitors of the synthesis of prostaglandins, while it is a powerful inhibitor of proinflammatory cytokines. For that reason, it can be classified as a Cytokine Suppressive Anti-inflammatory Drug (CSAID).

In addition to its anti-inflammatory activity, benzydamine shows local analgesic/anesthetic effects that in the topical route can be fully exploited and turned into competitive advantages over Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

In fact, its elective therapeutic use is the topical control of acute inflammation and pain. Benzydamine formulated as 0.15% mouthwash, 3 mg lozenges, 0.15% and 0.30% nebulizers, has its target indication in the symptomatic treatment of pain and irritative/inflammatory conditions of the oropharynx (gingivitis, stomatitis, pharyngitis), even when due to dental therapy, although it has also been largely used in various conditions ranging from post-tonsillectomy pharyngitis or radiomucositis, to throat irritation and/or dysphagia induced by intubation.

Benzydamine was widely used in clinical practice and, therefore consistent clinical experience together with a large amount of literature demonstrating its efficacy and tolerability, are available. The aim of this document is to summarize the pharmacological, pharmacokinetic and clinical data available on benzydamine.
The chemical structure of benzydamine hydrochloride, or N,N-dimethyl-3-{[1-(benzyl)-1H-indazol-3yl]oxy}-1-proponamine hydrochloride differs from that of conventional NSAIDs. It is a white crystalline powder, very soluble in water, freely soluble in ethanol (96%) and in chloroform, and practically insoluble in ether.

The molecular formula is \( \text{C}_{19}\text{H}_{23}\text{N}_3\text{O} \cdot \text{HCl} \). It has a molecular weight of 345.9 and a melting point of 158.5 – 160.0 °C.

Figure 1: structural formula of benzydamine hydrochloride.
3. CSAID Benzydamine vs. NSAIDs

Although benzydamine is a non steroidal anti-inflammatory agent, it possesses a different mechanism of action that distinguishes it from conventional NSAIDs.

The main feature that differentiates benzydamine from aspirin-like drugs is its mechanism of action. Unlike, NSAIDs, which derive their anti-inflammatory effects by inhibiting the synthesis of prostaglandins, benzydamine inhibits the production of proinflammatory cytokines, mainly TNF-α, and to a lesser extent IL-1β and MCP-1. Thus, benzydamine, can be fully considered a CSAID.

Since benzydamine lacks significant inhibition against prostaglandins it does not produce the characteristic side-effects of aspirin-like drugs (Figure 2). Benzydamine, in fact, inhibits prostaglandins synthesis in vitro only at concentrations which are not reached in vivo (200-400 µg/ml) following both local and systemic administrations.

Following topical applications benzydamine shows local anesthetic properties, not common among other NSAIDs, which in topical use allows benzydamine to exert an immediate effect on pain.

Figure 2 summarises the main features and advantages displayed by the CSAID benzydamine compared to NSAIDs.
4. **PHARMACOLOGY**

Benzydamine is a Cytokine Suppressive Anti-inflammatory Drug, which is devoid of activity on arachidonic acid metabolism and has local anaesthetic and analgesic properties.³

On the contrary to the systemic administration, the local application of benzydamine produces higher concentrations in the inflamed area than in the blood, as demonstrated in animals and humans.¹⁰,¹¹ The capability of benzydamine to concentrate in the inflamed tissues, with low systemic exposure, represents a clear advantage by limiting potential systemic side effects.⁸ In addition, the benzydamine topical preparations show additional pharmacological effects, such as a local anaesthetic effect, that cannot be obtained through systemic administration.¹²

4.1 **PHARMACOKINETICS**

Mouthwash, oral spray and lozenges are oropharyngeal formulations intended to exert local effects in the oral cavity and/or throat, even if detectable drug plasma levels have been reported after topical administrations, probably related to absorption through the oral mucosa.¹³

After a single administration of 0.15% benzydamine solution by ingestion (25.5 mg benzydamine/70 kg), gargle (102 mg benzydamine/70 kg), and spray (about 12 mg benzydamine),¹⁴ detectable drug plasma concentrations were observed in all subjects. After ingestion, the drug levels were clearly much higher than in either of the two other treatments. The mean plasma concentration time curves for each benzydamine treatment are shown in Figure 3.

![Figure 3: mean plasma concentration time curves of benzydamine following ingestion, gargle and spray.¹⁴](image-url)
After repeated benzydamine doses by ingestion, gargle, and spray, no significant accumulation of the drug was observed in plasma. As reported after single administration, the benzydamine level in plasma differed between treatments, with the spray and gargle benzydamine AUCs lower than that observed after drug ingestion.\textsuperscript{14}

Pharmacokinetic assessment of benzydamine 0.15% mouthwash obtained after gargling with a 15 ml dose (6 gargles every two hours), and after ingestion of a single 15 ml dose showed that the systemic benzydamine bioavailability after multiple gargling was approximately 16% in comparison to the single dose ingestion.\textsuperscript{15}

After the administration of a single 3 mg benzydamine lozenge, peak plasma values of 37.8 ng/ml with an AUC of 367 ng/mlh were observed approximately 2 hours after administration.\textsuperscript{13} These levels are not sufficient to produce systemic pharmacological effects.\textsuperscript{16}

Excretion occurs mainly through urine and is mostly in the form of inactive metabolites or conjugation products.\textsuperscript{17}

\section*{4.2 Pharmacodynamics}

Benzydamine is a cytokine suppressive anti-inflammatory drug\textsuperscript{2} with anti-inflammatory, analgesic and local anaesthetic effects. It is also reported to have a degree of antibacterial and antifungal activity \textit{in vitro}.\textsuperscript{8}

\subsection*{4.2.1 Anti-inflammatory activity}

The main mechanism of action responsible for the anti-inflammatory effect of benzydamine is its inhibitory activity on the production of cytokines.\textsuperscript{2} However, benzydamine exerts other activities that may contribute to its anti-inflammatory effect, such as reducing the perfusion flow and vascular permeability produced by histamine, acetylcholine, serotonin and epinephrine, the inhibition of platelet aggregation, thrombus formation, degranulation of human polymorphonuclear leukocytes, and inhibition of the migration of human monocytes.\textsuperscript{10, 18, 19, 20}

\begin{itemize}
\item \textbf{Effects on cytokines}
\end{itemize}

In pharmacodynamic investigations, performed \textit{in vitro} on mononuclear cells of humans and mice exposed to different inducers such as lipopolysaccharide (LPS) and \textit{Candida albicans}, benzydamine was shown to inhibit TNF-\(\alpha\) production and to a lesser extent IL-1\(\beta\) and MCP-1, whereas it did not affect IL-6 and IL-8 production.\textsuperscript{2, 3}

Data demonstrating this selective inhibitory effect of benzydamine on cytokine production in human mononuclear cells stimulated by \textit{Candida albicans} are reported in Table 1.\textsuperscript{3}

Benzydamine (6.25-50 µM) produced a dose-dependent reduction in TNF-\(\alpha\) and MCP-1. The release of IL-1\(\beta\) decreased with benzydamine concentrations up to 25.0 µM, while no clear effects on the release of IL-6 and IL-8 were observed.\textsuperscript{3}
Importantly, in the same cells stimulated with LPS and under conditions where TNF-α and IL-1β were decreased by benzydamine, the drug did not modify the production of cytokines with anti-inflammatory proper-
ties, such as IL-10 and IL-1ra.

It is worth noting that unlike benzydamine, NSAIDs such as ibuprofen and naproxen were definitely powerless in the suppression of inflammatory cytokine production from Candida activated mononuclear cells. Figure 4 shows the effects of different concentrations (12.5, 25 and 50 µM) of these two drugs on TNF-α and MCP-1 production in comparison to the same concentrations of benzydamine.

<table>
<thead>
<tr>
<th>Benzydamine</th>
<th>Candida albicans-induced production of</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNF-α (ng/ml)</td>
<td>IL-1β (pg/ml)</td>
<td>IL-6 (U/ml)</td>
<td>IL-8 (ng/ml)</td>
<td>MCP-1 (ng/ml)</td>
</tr>
<tr>
<td>Medium</td>
<td>7.6 ± 1,6</td>
<td>73,01 ± 6,46</td>
<td>419 ± 105</td>
<td>2.99 ± 0.22</td>
<td>1.56 ± 0.21</td>
</tr>
<tr>
<td>6.25 µM</td>
<td>ND</td>
<td>51,82 ± 6,02</td>
<td>354 ± 73</td>
<td>2.48 ± 0.26</td>
<td>1.14 ± 0.24*</td>
</tr>
<tr>
<td>12.5 µM</td>
<td>6.4 ± 0.9</td>
<td>47,20 ± 3.24*</td>
<td>316 ± 91</td>
<td>2.78 ± 0.31</td>
<td>1.03 ± 0.22**</td>
</tr>
<tr>
<td>25.0 µM</td>
<td>4.9 ± 0.5**</td>
<td>39,52 ± 4.19**</td>
<td>656 ± 80**</td>
<td>2.57 ± 0.12</td>
<td>0.72 ± 0.06**</td>
</tr>
<tr>
<td>50.0 µM</td>
<td>1.9 ± 0.2**</td>
<td>66,20 ± 5.66</td>
<td>353 ± 307</td>
<td>2.77 ± 0.29</td>
<td>0.64 ± 0.05**</td>
</tr>
</tbody>
</table>

ND= Not Determined
P<0.05 vs. medium, ** P<0.01 vs. medium by Dunnett’s test

1) Results are from one representative normal subject of the five (TNF-α, IL-1β, IL-6 and IL-8) or six (MCP-1) examined

**Table 1:** effect of benzydamine on cytokine and chemokine production by peripheral blood mononuclear cells.

**Figure 4:** activity of benzydamine, ibuprofen and naproxen on TNF-α and MCP-1 production by Candida albicans-stimulated peripheral blood mononuclear cells (Adapted from Sironi et al.).
Benzydamine confirmed its suppressive effect on these cytokines, while neither ibuprofen nor naproxen significantly reduced the amount of TNF-α and MCP-1 secreted from Candida-treated human cells.\(^3\)

**Effects on chemotaxis**

Benzydamine exerts an inhibitor activity on monocyte chemotaxis, a function shared by immune cells and crucial in inflammation.\(^20\)

As shown in *Figure 5*, chemotactic activation is mediated by binding a chemotactic agonist to trans-membrane receptors and results in the activation of multiple signaling proteins and second messengers. The activation of mitogen-activated protein kinase (MAPKs), such as extracellular-signal-regulated protein kinases 1/2 (ERK) and p38 MAPK seems to be one of the key components in signal transduction associated with cell migration.\(^21\)

Riboldi *et al.*\(^20\) showed that benzydamine inhibited the migration of inflammatory leukocytes, and this effect was associated with a strong inhibition of the MAPK pathway. In particular, benzydamine strongly inhibited chemoattractant-induced activation of...
both ERK1/2 and p38 MAPK pathways implicated in cell migration.

These results suggested that the benzydamine inhibitory effect on monocyte chemotaxis most likely contributes to its anti-inflammatory activity. 20

• Effects on the production of prostaglandins

It has been shown that prostaglandin biosynthesis is stimulated by cytokines such as IL-1 and TNF-α in various types of cells, including gingival fibroblasts. When the cells were treated simultaneously with benzydamine and IL-1β or TNF-α, the drug significantly reduced the stimulatory effect of these cytokines on prostaglandin E₂ (PGE₂) production as well as significantly reduced the production of prostaglandin I₂ (PGI₂). 22

This capability of benzydamine to reduce prostaglandin production induced by IL-1β or TNF-α in gingival fibroblasts may confirm the rationale for the use of the drug in controlling inflammatory oropharyngeal conditions.

4.2.2 Local anaesthetic activity

Following topical applications, benzydamine shows local anaesthetic properties. 7

In a clinical trial performed on 87 healthy subjects benzydamine, when applied topically to normal mucosa for 60 seconds, was found to exert a remarkable anaesthetic activity that was superior to the control (cetylpyridinium hydrochloride 0.025%) and placebo mouthwashes, showing also a long lasting effect (more than 90 minutes). 7 The local anaesthetic activity of benzydamine has been shown to be extremely useful in the treatment of painful mouth and throat conditions, mainly due to rapid pain relief. 23

These local anaesthetic properties demonstrated by benzydamine are most probably due to its structural features. In fact, the drug shares with local anaesthetics an aromatic (hydrophobic) ring structure, linked to a basic tertiary amine group (hydrophilic) by a short alkyl chain (Figure 6). Therefore, benzydamine similar to as local anaesthetics, reversible block nerve conduction when topically applied in appropriate concentrations. 24

4.2.3 Antimicrobial activity

Bactericidal activity of benzydamine (drug concentrations ranged from 10 to 1280 µg/ml) was determined against 110 bacterial strains clinically isolated in Spain. For all the bacteria studied, the MICs observed, between 320 and 1280 µg/ml, were lower than benzydamine concentration in the marketed product (1500 µg/ml). 25

The fungistatic and fungicidal activity of benzydamine against Candida-albicans and non-albicans strains (20 Candida strains: 18 clinical isolated and two American Type Culture Collection strains) were also investigated. At lower concentrations ben-
zydamine inhibited growth in all Candida strains studies (fungistatic activity), with MIC ranging between 6.25-50 µg/ml, while at higher concentrations (0.2 mg/ml) it is a fungicidal due to its direct damage to the cytoplasmic membrane. The benzydamine concentration in oral solutions (0.15% mouthwash and spray) is 30 times higher than the MIC of the least susceptible Candida strains.  

Figure 6: structural features of benzydamine shared with the known local anaesthetics.
Therapeutic Rationale

Benzydamine has been largely used in symptomatic treatment of pain, irritation and inflammation of the oropharynx, even when due to dental therapy, although it has also been largely used for various conditions ranging from post-tonsillectomy pharyngitis or radiomucositis, to throat irritation and/or dysphagia induced by intubation.

The main characteristics that make topical benzydamine (0.15% mouthwash, 0.15% and 0.30% oropharyngeal spray and lozenges) useful in the treatment of inflammatory and painful disorders are hereinafter presented.

The amount of available clinical data on the efficacy and safety of benzydamine is very extensive. Clinical trials hereinafter presented are the most representative studies with the mouthwash, oropharyngeal spray and lozenges formulations in adults and children affected by various local mouth and throat inflammatory conditions.

5.1 PAINFUL INFLAMMATORY CONDITIONS OF OROPHARINX TRACT

The effectiveness of benzydamine 0.15% mouthwash in relieving throat pain and dysphagia has been shown in different studies. In comparison to the placebo, benzydamine displays a significantly better reduction of pain with a more rapid decrease of pain severity over a 2-day period.\(^\text{27}\)

Patients with acute pharyngitis, rhinitis, and tonsillitis instructed to gargle with 15 ml of mouthwash containing benzydamine (every 1.5-3 hours for 7 days) experienced a greater reduction of pain and burning sensations starting from the 2\(^{\text{nd}}\) day of therapy, as compared to placebo-treated patients. Dysphagia, otalgia, and sensation of hypoacusia also appeared to significantly improve in the group treated with benzydamine. In addition, a reduction in hyperemia and oedema of the pharynx, as well as in hypertrophy of the lymph nodes, was observed from the 1\(^{\text{st}}\) day of treatment in benzydamine-treated patients.\(^\text{28}\)

Schachtel et al. confirmed these findings in two more placebo-controlled clinical trials involving a total of 283 adults patients with acute sore throat.
Patients were treated with benzydamine 0.15% mouthwash (15 ml dose every 2-4 hours up to 6 times daily for up 7 days) or placebo.\textsuperscript{29,30}

Results of efficacy parameters (difficulty swallowing scale, change in pain scale, and sore throat relief scale) assessed in the first study, are reported in Table 2.\textsuperscript{29}

Benzydamine was able to rapidly relieve the characteristic symptoms of sore throat, such as pain on swallowing and pharyngeal inflammation by virtue of its topical effects.\textsuperscript{29} Similar results were obtained in the second trial with the exception of the difficulty in swallowing scale.\textsuperscript{30}

The effectiveness of benzydamine oropharyngeal spray in the treatment of acute or recurring chronic tonsillitis without concurrent antibiotic therapy, was compared with an association containing the antiseptic hexamidine plus an anaesthetic local tetracaine.

<table>
<thead>
<tr>
<th>EFFICACY VARIABLES</th>
<th>MEAN IMPROVEMENT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty swallowing scale (VAS 0 to 100mm)</td>
<td>Benzydamine (N=63) 25.9 mm</td>
<td>15.8 mm 0.018</td>
</tr>
<tr>
<td>Change in pain scale (VAS 0 to 100mm)</td>
<td>27.4 mm</td>
<td>18.6 mm 0.062</td>
</tr>
<tr>
<td>Sore throat relief scale (0=none to 6=complete)</td>
<td>1.9 units</td>
<td>1.3 units 0.023</td>
</tr>
</tbody>
</table>

Table 2: overall mean improvement after benzydamine and placebo treatments in the intent-to-treat population.

Treatments showed a comparable effectiveness, good tolerability and palatability, even if a quicker and intense improvement was obtained with benzydamine.\textsuperscript{31}

Benzydamine 0.15% mouthwash, thanks to its proven effectiveness and extensive use in the topical treatment of oral inflammatory and painful conditions, was chosen as reference product in two clinical studies. These were performed with the aim of demonstrating the therapeutic equivalence of benzydamine 3 mg lozenges with the mouthwash formulation, in the treatment of oropharyngeal disease.\textsuperscript{32,33}

Efficacy parameters were evaluated according to a 4-point scale (0=no symptomatology to 3=severe symptomatology). Results of these studies are shown in Figures 7-8.
In both studies, a clear improvement/reduction of symptoms was observed with no statistically significant differences between the two benzydamine oropharyngeal dosage forms.\textsuperscript{32,33} The efficacy of 3 mg benzydamine lozenges and its good tolerability were further confirmed in a controlled clinical study that included a large number of patients (N=120) with acute or chronic disorders of the respiratory tract characterized by cough and inflammatory symptoms of the oropharynx. Benzydamine 3 mg lozenges, dextromethorphan 7.5 mg lozenges and their combination were administered t.i.d for a period of 15 days. Benzydamine produced a progressive clinical improvement in symptoms and signs caused by the inflammatory process. The cough symptom and the average number of cough, were significantly reduced only in the groups treated with the association and dextromethorphan. Systemic and local tolerability of the treatments was excellent.\textsuperscript{34}

\textbf{Figure 7: mean score for the evaluated signs and symptoms of the oropharyngeal disease recorded at basal and subsequent observation times (Adapted from De Vita).}\textsuperscript{32}
The pharmaceutical form of tablets, to be dissolved in the mouth, was very well accepted because of its simple administration, which improved patients' compliance. Lozenges also have an advantage over sprays and gargles which is that of being slow-releasing, thereby continuously delivering the drug to the affected areas of the throat.  

Thus, 3 mg benzydamine lozenges may represent a useful alternative to mouthwash, especially in those cases in which a more convenient pharmaceutical preparation may facilitate the patients' compliance, contributing to a superior therapeutical result.

5.2 ODONTO-STOMATOLOGIC CONDITIONS

The efficacy of benzydamine, in terms of pain relief, has also been proven in the treatment of patients suffering from diseases of the periodontium and oral mucosa.  

In periodontal disease, the main etiologic factor is dental plaque. Plaque can be removed by brushing and flossing, but
patient’s compliance with oral hygiene regimens is often very low. Thus, a mouthwash capable of reducing plaque and inflammation would be a valuable aid in treating and preventing periodontal diseases.

The efficacy of a 7-day treatment with benzydamine alone (3-4 times a day) in reducing plaque formation had been previously demonstrated in two double-blind, placebo-controlled clinical studies. Significant improvements were demonstrated with benzydamine compared to placebo in all the efficacy parameters tested: plaque index, gingival index, healing, and pain reduction.

Although the above results are very interesting, benzydamine 0.15% mouthwash is mainly used in the treatment of different pathologies of the oral cavity, including effects due to dental therapy.

In patients (N=106) with chronic periodontitis undergoing removal of dental deposits, the treatment with benzydamine 0.15% mouthwash produced a statistically significant decrease in mean pain intensity (Figure 9). Benzydamine, therefore, proved its beneficial effects also on pain due to conservative dental therapy.

The therapeutic efficacy and local tolerability of benzydamine 0.15% oropharyngeal spray was demonstrated in comparison to placebo in patients with various odonto-stomatological conditions (such as gingivitis, dental extractions, post-extraction wounds, peri-coronal inflammations, excision of dental operculum and excision of papillomas). Benzydamine 0.15% oropharyngeal spray (4 nebulisations, 6 times daily for 4 days) was able to alleviate patients’ discomfort with a significant improvement of symptoms and signs starting from the 1st treatment day. By the last day of treatment all signs and symptoms disappeared with a highly significant difference in favour of the benzydamine group (p<0.001).

Similarly, a very good clinical efficacy was observed following treatment with benzydamine oropharyngeal spray and mouthwash in patients with oral erosive and ulcerative lesions that appeared during the course of various diseases. The symptomatology improved evenly in 74% of patients treated with oropharyngeal spray and mouthwash after 3-4 days of administrations. It is important to note that in case...
of single lesions benzydamine oropharyngeal spray formulation is the most simple to use, since it allows a precise application of the drug.\textsuperscript{37}

5.3 \textbf{USE IN PARTICULAR INFLAMMATORY CONDITIONS OF THE ORAL CAVITY}

Sore throat and/or dysphagia are often reported by patients with nasal-gastric intubation or undergoing tracheal intubation during general anaesthesia. In fact, nasal-gastric or tracheal intubation and direct local surgical procedures involving mouth, gums and throat often produce inflammatory conditions of the oropharynx. Benzydamine was also widely used in the treatment of aphthous ulcers and oral mucositis, a frequent complication of head and neck radiotherapy.\textsuperscript{8}

- Pharyngo-laryngeal pathology following intubation

Twenty four to ninety percent of patients who receive general anaesthesia and endotracheal intubation suffer from postoperative sore throat.\textsuperscript{43} Benzydamine mouthwash and oropharyngeal spray applied both before and after surgery have been shown to be effective in reducing the incidence and severity of the postoperative sore throat.

Pre-emptive treatment with benzydamine mouthwash and oropharyngeal spray has been reported to decrease the incidence and severity of sore throat due to endotracheal intubation.\textsuperscript{43,44} These findings were confirmed in a comparative clinical trial. In this study, gargling with benzydamine (0.15\% mouthwash, 15 ml dose made into 30 ml with distilled water) reduced the incidence of postoperative sore throat for up to 24 hours, while dispersible aspirin gargles (350 mg tablet made into 30 ml with distilled water) only up to 2 hours.\textsuperscript{45}

Two previous placebo-controlled studies proved that benzydamine has a marked therapeutic effect in the treatment of inflammatory lesions due to nasal-gastric and endotracheal intubation.

Patients with sore throat and/or dysphagia due to the use of nasal gastric tube and patients that underwent endotracheal intubation received benzydamine 0.15\% mouthwash\textsuperscript{46} and 0.30\% spray\textsuperscript{47}, respectively. The dosages scheduled consisted of 15 ml dose of benzydamine every 2-3 hours for 1-2 days or of 10 nebulizations of benzydamine spray every 3 hours for 3 days. Significant relief of pain and dysphagia was recorded in favour of benzydamine, with an improvement in signs and symptoms clinically and statistically superior to that observed in the placebo group. The improvement was evident starting from Day 2, with the complete resolution of symptomatology on Day 3.

- Pharyngitis post-tonsillectomy

Tonsillectomy, a surgical procedure commonly performed in children and young adults, may often produce dysphagia, sore
throat and earache in the early post-operative period.\textsuperscript{48}

Many studies performed on adult tonsillectomized patients have shown the therapeutic efficacy of benzydamine, particularly when topically administered as 0.15% mouthwash (5 times daily for 7 days)\textsuperscript{49} or as 0.15% oropharyngeal spray (2 nebulisations from 3 to maximum 8 times day for 3 days)\textsuperscript{48}. Evidence of benzydamine's analgesic action was provided by its capability in relieving throat pain and in difficulty in swallowing, whereas evidence of benzydamine's anti-inflammatory action was given by its high effectiveness in improving clinical symptoms (hyperemia, edema and feelings of "blocked ears").\textsuperscript{49}

The efficacy of benzydamine 0.15% mouthwash (gargles every 3 hours) in the post-operative management of tonsillectomy was also assessed in comparison with soluble aspirin (gargles every 3 hours and then swallowed). Aspirin proved to be slightly more effective in relieving pain and discomfort of swallowing, while benzydamine oral rinse was superior in the relief of earache, in promoting the healing of the tonsil seat, with a shorter duration of the treatment need.\textsuperscript{50}

\textbf{Oral radiation mucositis}

Patients who undergo radiation therapy to the head and neck often develop mucositis of the oropharynx that produces oral pain and may limit food intake.\textsuperscript{51} In more than half of patients with mucositis, the condition is so severe that it requires parenteral analgesia, interruption of radiation therapy, and/or hospitalization and the need for parenteral or tube feeding.\textsuperscript{52}

The biology of ulcerative mucositis involves the sequential interaction of cells, cytokines and the oral microflora. The initial tissue response to radiation appears to be the release of a number of pro-inflammatory cytokines including IL-1, IL-6 and TNF-\(\alpha\).\textsuperscript{52} Benzydamine inhibits the production of such pro-inflammatory cytokines, particularly TNF-\(\alpha\), and IL-1\(\beta\),\textsuperscript{2-4} therefore limiting radiation mucositis through its ability to suppress selected proinflammatory cytokine production.\textsuperscript{52}

Preliminary experiences to define the therapeutic potency of benzydamine oral rinse in this inflammation of the oral mucosa were performed in the 80's. In 1998 benzydamine was added to the US FDA Orphan Drug List with the orphan designation for the prophylactic treatment of oral mucositis resulting from radiation therapy for head and neck cancer.

Two earlier studies suggested that benzydamine was effective in reducing the severity of the pain associated with oral mucositis.\textsuperscript{53,54} Subsequent single and multicenter trials proved that topical benzydamine reduces the frequency and severity of ulcerative oral lesions and decreases pain in radiation-induced oral mucositis.\textsuperscript{51,52,54-57}

The results of a large, multicenter, double-blind, randomized trial published in 2001,
demonstrated that treatment with 0.15% benzydamine mouthwash improved the ulcer-free rate and diminished the incidence of ulceration and erythema. These findings were observed in 172 patients (84 benzydamine, 88 placebo), treated for 2 minutes 4-8 times daily before and during radiation therapy, and for 2 weeks after completion of radiation therapy. The study also demonstrated a delay in the need for rescue medications (analgesics) in patients who were treated with benzydamine compared with patients treated with placebo.52

As reported in a review of publications on the etiopathogenesis and prevention of oral mucositis commonly sequel of radiotherapy, chemotherapy, and radiochemotherapy, benzydamine, among the current available products, was shown to have the strongest scientific evidence of support for prophylaxis of mucositis.58

In Clinical Practice Guidelines published in 2004 by the American Cancer Society, benzydamine has been recommended in the prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiotherapy.59 This recommendation for the use of benzydamine in the prevention of radiation-induced mucositis was confirmed in the updated clinical practice guidelines published in the March 1, 2007 issue of Cancer.60

- Aphtous mouth ulcer
  Recurrent aphtous ulcers affect up to one fifth of the general population. Aphtous ulcers also called canker sores, aphtous stomata and aphtous stomatitis are among the most common oral lesions seen by dentist.8 This condition can be painful for the patient, making it uncomfortable to speak, eat and/or drink. Their aetiology, however, remains uncertain and treatment is mainly symptomatic or with anti-inflammatory agents.61

  Studies performed to evaluate benzydamine 0.15% mouthwash in the treatment of aphtous ulcers suggest that it may be useful in reliving pain associated with these lesions. In fact, in a placebo comparative study performed on patients with aphtous ulcers, 61% of the subjects receiving benzydamine experienced a reduction in pain severity of at least 50%, as compared to 22% of the patients on placebo.62 A preference for benzydamine treatment was expressed by patients by virtue of its local anaesthetic effect responsible for some pain relief.23

  In a study examining the subjective efficacy of the 38 proprietary agents commonly used for aphtous treatment, benzydamine 0.15% mouthwash appeared to provide the best pain control and symptomatic relief to patients with oral aphthae.61

- Burning mouth syndrome
  Burning mouth syndrome is a source of oral discomfort, mainly occurring in middle-aged or elderly women, without an identifiable local pathology. In a pilot clinical trial, patients with stomato-glossopyrosis rinsed for 10 days with benzydamine mouthwash
or placebo, and assessed their pain, mouth dryness and burning sensation by means of visual analog scale (VAS). Differences were found between the two groups favouring the benzydamine containing solution.

5.4 USE IN CHILDREN
Children are less open to tolerate pain than adults even if, from a pharmacological point of view, it should be stated that children cannot be merely considered as little adults. Topical treatments in part overcome this issue, in view of the fact that everything should be done to lessen discomfort in children. In particular, oral topical treatments may represent a clear advantage in young patients with painful conditions of the oropharynx, especially when dysphagia represents a limiting step in the ingestion of any oral medication.

Topical benzydamine, in virtue of its well-known anti-inflammatory properties and rapid pain control, is a valid therapeutic tool in the medication of children.

In a placebo-controlled clinical trial performed in 146 children (4 to 17 years) with sore throat, Schachtel et al. demonstrated the efficacy of benzydamine 0.15% mouthwash. One single 15 ml dose of benzydamine 0.15% mouthwash was significantly better (p<0.05) than placebo in all efficacy parameters (Figure 10), namely Children's Sore Throat Pain Thermometer (VAS 0 to 200 mm), Children's Sore Throat Relief Scale (Scale 0 to 4 units) and Nurse's Change-in-Pain Scale (VAS 0 to 100 mm). Efficacy evaluations were performed at 5-minute intervals over a 1-hour evaluation period.

When gargling with benzydamine mouthwash presents technical difficulties, such as in the case of small children, benzydamine can be successfully administered as oropharyngeal spray or lozenges.

![Figure 10: efficacy assessment after treatment with a single 15 ml dose of benzydamine 0.15% mouthwash or placebo.](image)
The effectiveness of benzydamine 3 mg lozenges was proven in comparison with benzydamine 0.15% mouthwash in a patient population (age range 4-67 years) that also involved children, affected by oropharyngeal disease. Benzydamine lozenges showed comparable therapeutic efficacy and tolerability with respect to the mouthwash, with no statistically significant differences between formulations.32

Benzydamine 0.15% oropharyngeal spray administered to children (age range 4-12 years) with sore throat proved to be an effective, acceptable and throuble-free treatment for sore-throat in younger patients which, in most cases were eased from the pain.65

According to the easy route of administration, particularly in younger patients, benzydamine 0.15% oropharyngeal spray has been effectively used in the post-operative course of children and adolescents undergoing adenotonsillectomy. A significant reduction in the intensity of local pain (pharyngodynia) and/or of pain at swallowing, already 24 hours after surgery (Figure 11), was observed in young patients (aged 3 to 17 years) treated with benzydamine in comparison to placebo (4 nebulisations up to 8 times a day for 6 days). The intensity of the symptoms pharyngodynia, dysphagia, and if any otalgia was graded with a 4-point score from 0 (no pain) to 3 (remarkable pain).66

Studies involving children suffering from post-operative pain following tonsillectomy showed that benzydamine was effective in the relief of typical discomfort, within a few days. Benzydamine produced a significantly faster and greater improvement than placebo and was also significantly superior in the overall therapeutic effect.67-69

Figure 11: Symptom course during treatment (4 nebulisations in up to 8 times a day for 6 days) with benzydamine and placebo (adapted from Fior et al.)66
Benzydamine mouthwash, oropharyngeal sprays and lozenges are medicinal products for topical use, and since very modest systemic absorption occurs, systemic serious adverse effects are not expected. Benzydamine shows a very good safety profile, as confirmed in clinical trials and by post-marketing pharmacovigilance information.

An open study involving 7,618 patients with oropharyngeal diseases was performed with the objective of monitoring the frequency of side-effects following benzydamine oral local treatment. Benzydamine resulted to be well tolerated locally. No serious adverse event was reported, while 340 out of 7,618 patients (4.5%) reported not serious side effects.

The AEs recorded during the study and their incidences are reported in Table 3.

Numbness and burning were the most frequently reported side effects, most probably related to the local anaesthetic effect of benzydamine. In fact, the local anaesthetic activity of benzydamine is sometimes mistakenly interpreted as an adverse event. On the other hand, this is actually a very useful therapeutic characteristic of the drug, which provokes a mild sensation of numbness in the mouth capable of immediately relieving the local painful conditions. Other symptoms such as trouble swallowing, dry mouth sensation or increased salivation were rarely observed with benzydamine oral local treatment, as well as dryness of the mouth or hypersensitivity reactions. Laryngospasm and angioema were very rarely and photosensitivity was uncommon observed.

<table>
<thead>
<tr>
<th>RECORDED AEs</th>
<th>No. OF CASES</th>
<th>No. AEs /TOTAL AEs (%)</th>
<th>No. AEs / TOTAL PATIENTS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness, furry tongue, paraesthesia</td>
<td>134</td>
<td>39</td>
<td>1.7</td>
</tr>
<tr>
<td>Burning</td>
<td>85</td>
<td>25</td>
<td>1.1</td>
</tr>
<tr>
<td>Nausea, ratching, vomiting</td>
<td>44</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td>Bad taste</td>
<td>32</td>
<td>9</td>
<td>0.4</td>
</tr>
<tr>
<td>Dryness of the mouth / increased salivation</td>
<td>17</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>Taste disturbances, loss of appetite</td>
<td>7</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>6</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>4</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Sleep disturbance, tiredness</td>
<td>3</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Others (headache, hot feeling)</td>
<td>2</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>340</strong></td>
<td><strong>100</strong></td>
<td><strong>4.5</strong></td>
</tr>
</tbody>
</table>

*Table 3: rating of patients reporting AEs*
7. POST MARKETING EXPERIENCE

The updated post marketing pharmacovigilance data refers to the period between January 2005 and August 2008. 71,72

7.1 WORLDWIDE SALES AND CONSUMPTION

In this period, the estimated number of patients treated with benzydamine mouthwash, oropharyngeal spray and lozenges is reported in the following table. The available data for benzydamine 0.15% mouthwash, 0.15% and 0.30% oropharyngeal spray are jointly treated as “topical oromucosal pharmaceutical forms”.71,72

7.2 INCIDENCE OF ADVERSE EVENTS AND EVALUATION OF THE RISK/BENEFIT RATIO

The adverse events reported to the Pharmacovigilance Service of ACRAF S.p.A. in the period between January 2005 and August 2008 for benzydamine topical oromucosal pharmaceutical forms (mouthwash, 0.15% and 0.30% oropharyngeal spray) and benzydamine lozenges are summarized in the table. Available safety data on the active substance and information reported in literature confirmed the positive risk/benefit ratio of benzydamine when topically used in the treatment of painful and inflammatory conditions of mouth and throat.71,72

Table 4: estimated number of patients treated with benzydamine topical oromucosal pharmaceutical forms (mouthwash, oral spray) and lozenges

<table>
<thead>
<tr>
<th>Benzydamine treatment</th>
<th>Estimated number of patients treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical oromucosal pharmaceutical forms (0.15% mouthwash + 0.15% oropharyngeal spray + 0.30% oropharyngeal spray)</td>
<td>43,056,669</td>
</tr>
<tr>
<td>Lozenges</td>
<td>7,850,222</td>
</tr>
</tbody>
</table>

Table 5: adverse events reported to the Pharmacovigilance Service of ACRAF S.p.A. between January 2005 and August 2008

<table>
<thead>
<tr>
<th>Benzydamine treatment</th>
<th>3 mg lozenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical oromucosal pharmaceutical forms (0.15% mouthwash + 0.15% oropharyngeal spray + 0.30% oropharyngeal spray)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of events</th>
<th>Expected</th>
<th>Unexpected</th>
<th>TOTAL</th>
<th>Expected</th>
<th>Unexpected</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non serious</td>
<td>4</td>
<td>36</td>
<td>40</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4</td>
<td>39</td>
<td>43</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 5: During the period considered, no adverse events occurring in patients treated with benzydamine 0.15% mouthwash, 3 mg lozenges, 0.15% and 0.30% oropharyngeal spray were published in literature.


11. Andersson K, Larsson H. “Percutaneous absorption of benzydamine in guinea pig and man”. Arzneim Forsch 1974; 24: 1686-8


13. Bareggi S. “Studio farmacocinetico di confronto nel volontario sano tra dosi singole orali dell’associazione benzidamina+destrometorfano e dei soli componenti”. Università degli Studi di Milano, Milan, Italy. Unpublished (1994); English translation: Comparative pharmacological study in healthy volunteers on a combination of benzydamine + dextromethorphan and the individual components, administered orally in single doses


21. Chiou WF, Tsai HR, Yang LM, Tsai WJ. “C5a differentially stimulates the ERK1/2 and p38 MAPK phosphorylation through independent signaling pathways to induced chemotactic migration in RAW264.7 macrophages”. Int Immunopharmacol. 2004; 4(10-11): 1329-41


33. Di Maggio M. “Studio clinico controllato del ‘Tantum verde pastiglie’ in odontostomatologia”. Odontostomatologia Section, Civic Hospital of Avellino, Italy. Unpublished (1981); English translation: A controlled clinical study on “Tantum verde lozenges” in odontostomatology


with a nasal gastric tube”. Coon Rapids Clinic, Coon Rapids, Minnesota, USA. Unpublished (1978)


67. Young JR. "A comparative study of benzydamine hydrochloride ("Difflam" pump spray) and placebo as analgesics following tonsillectomy". Int J Tissue React. 1987; 9(2): 131-3


70. Engles I. "Vertraglichkeitsstudie mit Tantum Verde gurgellosung". Med Welt 1980; 49: 3-7; English translation: Compatibility study with Tantum Verde (gargle solution)

