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Review

PHARMACOLOGY OF BENZYDAMINE

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ABSTRACT

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Benzydamine is a topical anti-inflammatory drug which is widely available and used topically for the treatment of the mouth. It is also used as a gel for application to inflamed joints. It has physicochemical properties and pharmacological activities which differ markedly from those of the aspirin-line non-steroidal anti-inflammatory drugs. Benzydamine is a weak base unlike the aspirin-like drugs which are acids or metabolized to acids. A major contrast with the aspirin-like drugs is that benzydamine is a weak inhibitor of the synthesis of prostaglandins but it has several properties which may contribute to its anti-inflammatory activity. These properties include inhibition of the synthesis of the inflammatory cytokine, tumour necrosis factor-α (EC_{50}, 25 μmol/L). Inhibition of the oxidative burst of neutrophils occurs under some conditions at concentrations of 30 to 100 μmol/L, concentrations which may be produced within oral tissues after local application. A further activity of benzydamine is a general activity known as membrane stabilization which is demonstrated by several actions including inhibition of granule release from neutrophils at concentrations ranging from 3 to 30 μmol/L and stabilization of lysosomes. Lack of knowledge of the tissue concentrations of benzydamine limit the correlation between pharmacological activities in vitro and in vivo. The concentration of benzydamine in the mouthwash is 4 mmol/L but the concentrations in oral tissues have not been studied adequately. Limited data in the rat indicates that concentrations of benzydamine in oral tissues are approximately 100 μmol/L.

Keywords: benzydamine, NSAIDs

INTRODUCTION

Benzydamine hydrochloride is a local anti-inflammatory drug which has analgesic and antipyretic properties. Formerly administered as tablets for systemic use, it is currently available only for local application: for the relief of sore throats, a mouth gargle or pump spray is available; gel ointment preparations are applied to the skin to treat inflammation of the soft tissues, skin and joints. It is widely used and has negligible side-effects when used locally [1]. The mode of action of benzydamine has not been established although many pharmacological effects are known.

CHEMISTRY

Anti-inflammatory drugs are commonly organic acids or metabolized to acids but benzydamine is a base usually formulated as its hydrochloride salt. It is highly lipid soluble in the unionized form (log partition coefficient – octanol/water = 3.71) [2].

Benzydamine is fluorescent (excitation 306 nm; emission 362 nm) [3] and is detected fluorometrically in HPLC assays [4]. This absorbance and fluorescence in the ultraviolet region may be associated with a possible pharmacological effect. It has been suggested that benzydamine and related compounds may reduce the formation of cataract due to absorbance in the UV region or, by a molecular interaction with lens protein, reduce the UV damage [3].

PHARMACOKINETICS

When administered as a mouthwash, the recommended dose of benzydamine is 15 ml of a 4-mmol/L solution of the hydrochloride salt in water [4]. This high concentration is transient as the benzydamine solution is only used to rinse the mouth and the remaining material is diluted by saliva. Following a mouthwash administration of benzydamine to rats (1 mg/kg), tissue concentrations in the oral tissues are reported to be as high as 100 μmol/L [5]. The depth of diffusion of the drug into oral tissues is not known but it is probable that surface concentrations are higher than 100 μmol/L. Commercially available benzydamine mouthwash is typically pH 4.5–5.0 but is unbuffered, so should rise quickly to salivary pH which is about 7. Judging from the uptake of other weakly basic, lipid-soluble drugs into buccal tissue, only a limited amount should be absorbed into buccal tissue during the recommended 30 s of mouthwash application [6,7]. The predicted small amount of absorption into buccal tissue is confirmed by the poor systemic availability (5%). Peak plasma concentrations are obtained at about 3 h and reach 0.5 μmol/L (Table 1) [4].

TABLE 1
Pharmacokinetic parameters of benzydamine in man

Parameter	Value	Reference
Systemic clearance	170 ml/min	[8]
Volume of distribution	10 L	[8]
Terminal half-life	7.7 h	[8]
Peak plasma concentrations from mouthwash	0.05 μmol/L	[4]
Local oral concentrations from mouthwash	4 mmol/L	[4]
Peak plasma concentrations from oral dosage	1.5 μmol/L	[4]
Gastrointestinal absorption	Rapid and complete	[8]
Drug bound to plasma proteins	< 20%	[13]

Following the oral administration of 50 mg benzydamine, peak plasma concentrations of 1.5 μmol/L are obtained after 1.5 h [4]. Gastrointestinal absorption is rapid and almost complete (Table 1) [4,8]. The high oral absorption of benzydamine is consistent with its high lipid solubility and relatively low clearance, which is about one tenth of liver blood flow.

Cutaneous application of benzydamine produces slow and prolonged penetration through the tissue. Radiolabelled benzydamine cream applied to the skin of guinea pigs was absorbed to a limited extent, with 13.2% of the administered radioactive drug recovered in the urine [9]. Benzydamine is present in plasma and urine after the application of 100 mg of the drug to human skin but the extent of absorption is not known [9].

Following the application of 100 mg of benzydamine cream onto rat paws, carrageenin-induced paw oedema was reduced. Total tissue concentrations obtained were about 58 μmol/L although, as the drug may accumulate in the skin, the concentrations at the inflammatory site may be considerably lower [10]. There is conflicting data concerning the accumulation in inflamed tissues. It was reported that benzydamine accumulates preferentially in the inflamed rat paws [10,11] following topical application and oral administration, but another study found no such preferential uptake [12]. There is no data on the penetration of the drug into the joints after local application to human subjects.

The protein-binding capacity of benzydamine is less than 20% [13]. Because of its lack of protein binding and high lipid solubility in the unionized form, benzydamine should be freely diffusible into cells. Its volume of distribution is, in fact, somewhat greater than body water (Table 1), indicating some binding to tissues. Its distribution therefore resembles several other basic lipid-soluble drugs although it is taken up by tissues to a lesser extent than many other basic drugs.

Benzydamine is taken up by a variety of intact mammalian cell lines in vitro. Its uptake is reversible on washing the cells, indicating that the uptake is not due to covalent binding of the drug or its metabolites. After fractionation of the cells, most benzydamine is found in the microsomal fraction [14].

METABOLISM AND EXCRETION

There is conflicting data on the elimination of benzydamine. From two studies, it was reported that considerable amounts (50–65%) of the drug were excreted unchanged in the urine [15,16]. Other work, however, indicates that only 5% is excreted unchanged in urine [4,8]. The high lipid solubility of the base form of benzydamine should be associated with considerable passive resorption in the renal tubule and the latter figure appears the more likely. Several inactive oxidized metabolites are excreted in urine (Figure 1). One metabolite, benzydamine N-oxide, is present in plasma at a peak concentration of approximately 0.6 μmol/L [5]. Further metabolites may be present in plasma and it is of note that the half-life of total metabolites in plasma is longer than that of the parent compound [8].

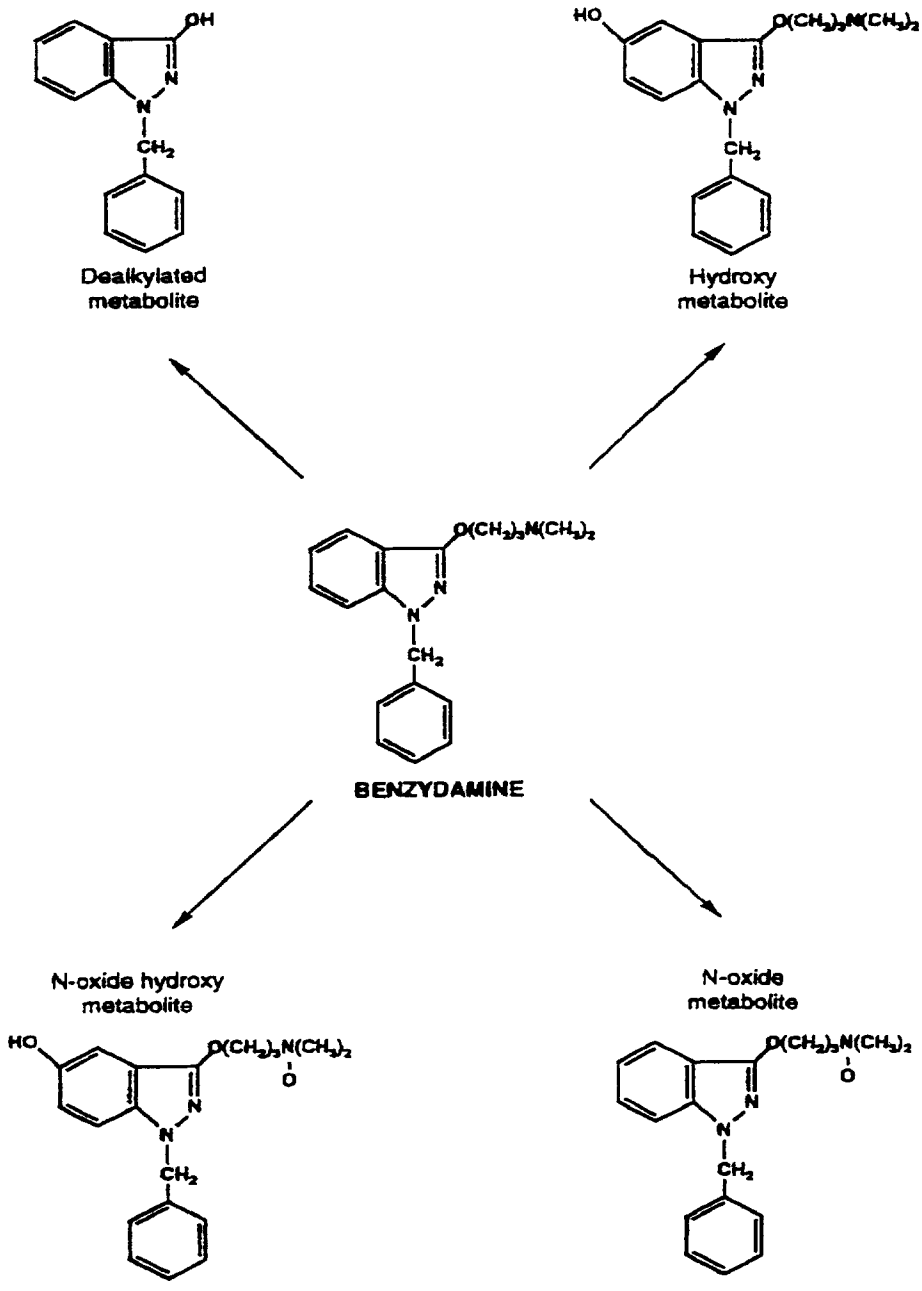

Figure 1. Metabolites of benzydamine. The formation of the N-oxide hydroxy metabolite requires two metabolic processes. (Redrawn from Schoenwald, Kumakura and Catanese [5])

ANTIBACTERIAL ACTIVITY

Benzydamine possesses non-specific antibacterial activity at the concentrations used as a mouthwash. It is active against strains resistant to broad-spectrum antibiotics, such as ampicillin, chloramphenicol and tetracycline, at a concentration of 3 mmol/L [17,18]. This property may prevent the development of secondary bacterial infections following viral-induced pharyngitis.

Combinations of benzydamine and certain antibiotics, most notably tetracycline, have a synergistic effect. Various strains of *Pseudomonas aeriginosa* and *Staphylococcus aureus*, including antibiotic-resistant strains, take up benzydamine quickly without any alteration to the integrity of their cytoplasmic membrane, as determined by the lack of leakage of proteins or polynucleotides. Benzydamine increases the bacterial uptake of antibiotics such as tetracycline and chloramphenicol and this effect may be responsible for the synergistic effects [17].

EFFECT ON INFLAMMATION

Anti-inflammatory effects in experimental animals

A number of properties of benzydamine resemble those of the non-steroidal anti-inflammatory group of drugs (NSAIDs). It reduces locally induced inflammation, oedema and granuloma formation in animals and demonstrates antipyretic and antiexudative activities. This aspect of its pharmacology has been extensively reviewed by White [19]. Benzydamine differs from other NSAIDs in that it acts on local factors of inflammation yet does not interact with systemic physiological mechanisms. Benzydamine does not, for example, inhibit the inflammation of multiple joints seen in adjuvant arthritis [20]. Possibly, insufficient concentrations are achieved in vivo for this effect to be observed. Further properties of benzydamine not usually associated with NSAIDs are its gastroprotective and local anaesthetic effects which are discussed below.

Benzydamine inhibits the venoconstriction of blood vessels by a variety of agonists, indicating a non-specific effect on the blood vessels rather than on specific receptors [10,21]. The vasodilation and increased vascular permeability induced by histamine are also inhibited by benzydamine [10]. Benzydamine may thus exert some of its anti-inflammatory activities by decreasing the vascular changes that may occur during inflammation.

Clinical

Topical application of 3% benzydamine cream is effective in the treatment of injuries, such as sprains and fractures. The effect of benzydamine on measures such as local heat, tenderness, spontaneous pain and oedema exeeds that of the placebo in double-blind studies [22,23]. No side-effects were noted [23].

Benzydamine mouthwash is effective in the treatment of tonsillitis and pharyngitis, with significant improvement in the associated pain and dysphagia in double-blind studies [24,25]. Benzydamine produces significant pain relief from oropharyngeal mucositis, which is a common side-effect following radiation therapy of the mouth [26]. It is also effective in pain relief from chemotherapy-induced mucositis, although minor side-effects of oral discomfort were reported. It appears that this analgesic activity is independent of its anti-inflammatory action as both patients with solid tumours and those with haematological malignancies who are unable to elicit a significant inflammatory response benefited [27]. Benzydamine is, however, ineffective in relieving pain following tonsillectomy [28] and has little impact on recurrent aphthous stomatitis, although it produced transient pain relief attributed to a local anaesthetic action [29].

The local application of benzydamine may usefully decrease the pain and inflammation following dental surgery. The oral administration of 50 mg benzydamine had no effect on pain and trismus following impacted molar extraction [30] although administration of a 1.5% oral spray produced analgesia following third molar extraction [31].

Effect on the metabolism of arachidonic acid

It is considered that the acidic NSAIDs, such as aspirin, exert their anti-inflammatory effects by inhibition of the synthesis of prostanoids. Benzydamine, by contrast, is only a weak inhibitor and the concentrations required to inhibit prostaglandin synthesis in vitro exceed those obtained following local or systemic administration (Table 2). Even

TABLE 2
Effects of benzydamine on the synthesis of arachidonic acid metabolites

Enzyme activity	Enzyme preparation	Approximate IC_{50}	Reference
Phospholipase	Human seminal plasma	0.3 mmol/L	[37]
Cyclo-oxygenase	Bull seminal vesicle	290 μmol/L	[33]
Endoperoxide synthesis	Ram seminal vesicles	700 μmol/L	[38]
Thromboxane synthesis	Horse platelet microsomes	290 μmol/L	[38]
Thromboxane synthesis	Human platelets	>1 mmol/L	[39]
Platelet aggregation	Rat platelets	100 μmol/L	[40]
$PGF_{2\alpha}$ and PGD_2 formation	Bovine seminal vesicle microsomes	1 mmol/L	[41]
PGE_2 formation	Bovine seminal vesicle microsomes	5 mmol/L*	[41]
Leukotriene synthesis	Mouse neutrophils	Inactive	[19]
Lipoxygenase	Bovine seminal vesicle	1.7 mmol/L	[33]

*Benzydamine increases formation of PGE_2 at lower concentrations

the concentrations in oral tissues are generally lower than those leading to inhibition of the synthesis of prostanoids.

A feature of the pharmacology of the aspirin-like NSAIDs is their gastrointestinal toxicity which is largely due to their inhibition of gastroprotective prostaglandins. Under some conditions, the synthesis of PGE_2 is actually enhanced by benzydamine. Consistent with its lack of significant inhibition on the synthesis of prostaglandins, benzydamine is not toxic to the gastrointestinal tract.

The ocular application of a 30-mmol/L solution of benzydamine reduces the concentrations of PGE_2 in aqueous humor after irritation of the cornea but this effect of benzydamine may be a consequence of the suppression of inflammation by a mechanism independent of any direct effect of cyclo-oxygenase [32].

In human seminal plasma, benzydamine inhibits the release of fatty acid precursors from membrane phospholipids and thus decreases the synthesis of prostaglandins, thromboxane and lipoxygenase products (Table 2). Benzydamine also inhibits lipoxygenase that may contribute to its actions as an anti-inflammatory agent [33]. It does not, however, inhibit the synthesis of leukotrienes, eliminating an action of 5-lipoxygenase [34,35]. Rather, benzydamine is reported to reduce the synthesis of hydroxyeicosatetraenoic acid, a product of lipoxygenase involved with leukotaxis [19]. Therefore, the effect of benzydamine is most likely on 12-lipoxygenase, which is involved in the synthesis of hydroxyeicosatetraenoic acid, rather than on 5-lipoxygenase which is involved in leukotriene synthesis [36].

ENZYMATIC EFFECTS

Benzydamine has a very small number of recorded effects on enzymes, other than those involved with prostaglandin synthesis or the oxidative burst of neutrophils or monocytes. In isolated fat cells stimulated with noradrenaline, benzydamine reduces lipolysis via the direct inhibition of hormone-sensitive triglyceride lipase ($IC_{50} = 0.3$–0.4 mmol/L) [42]. It also inhibits glucosamine-6-phosphate synthase, an enzyme involved in the synthesis of mucopolysaccharides [43] but the concentrations required are very high, 2–4 mmol/L, and are unlikely to be produced within any tissues.

EFFECT ON INFLAMMATORY CELLS

Direct effect on the inflammatory cells may contribute to the anti-inflammatory effect of many drugs. Two important responses by phagocytes that play a role in inflammation are the release of lytic enzymes, a consequence of degranulation, and the respiratory burst [44]. Benzydamine may inhibit both these responses by phagocytes. Inhibition of the release of granules and lytic enzymes is included in a general phenomenon termed membrane stabilization. This membrane-stabilizing activity may account for some of the anti-inflammatory properties of benzydamine.

Granule release

The inhibition of neutrophil degranulation and lytic enzyme release may be attributed to the membrane-stabilizing activity of benzydamine. Benzydamine decreases the release of specific granules of human neutrophils stimulated with phorbol myristate acetate, PMA, or calcium ionophore, A23187, with a strong inhibition seen at 30 μmol/L [44]. Benzydamine also inhibits azurophil granule release when neutrophils are treated with cytochalasin B and stimulated with N-formyl-methionyl-leucyl-phenylalanine, fMLP [19,44]. As degranulation is likely to occur during inflammation, the anti-inflammatory activity of benzydamine may be a result of its ability to inhibit this [19]. In introductory experiments, we have found that benzydamine also inhibits the degranulation of rat basophilic leukaemic cells, a mast cell-like line. The EC_{50} is approximately 200 μmol/L.

Cytokine and histamine release

Benzydamine inhibits the production of tumour necrosis factor-alpha (TNF-α) by stimulated human monocytes (IC_{50} 25 μmol/L). The effect is associated with a reduction in mRNA. There is no significant impact on the production of interleukins (IL), IL-1, IL-6 and IL-8, in these in-vitro experiments using human monocytes; however, with mouse peritoneal macrophages, IL-1 and TNF-α are both inhibited. In-vivo treatment of mice with benzydamine protects against lipopolysaccharide-induced septic shock, which may be attributed to the reduction of TNF-α and IL-1 in serum [45].

Respiratory burst of neutrophils, monocytes and macrophages

There has been some investigation into the effect of benzydamine on the respiratory burst of phagocytic cells although much of the data is incomplete, with little study on human cells (Table 3). The most detailed study is that of Baggiolini et al. who found inhibition of the oxidative burst under some conditions (Table 3) [44]. The maximal concentrations used to examine the effects of benzydamine on superoxide production by neutrophils was only 30 μmol/L; higher than those attained in plasma after oral dosage but lower than expected in oral tissues after local application and much lower than within the mouth. Superoxide production by neutrophils is inhibited by 30 μmol/L benzydamine when the cells are pretreated with cytochalasin B and stimulated with fMLP but not when the cells are stimulated with PMA. Benzydamine only slightly inhibits the respiratory burst of monocytes and macrophages (Table 3).

Benzydamine was found to inhibit lucigenin-dependent chemiluminescence of mouse neutrophils with lesser inhibition of luminol-dependent chemiluminescence [46]. The reported inhibition of chemiluminescence is, however, difficult to interpret as the effect of benzydamine was measured on the total chemiluminescence measured both before and after stimulation [46].

TABLE 3
The effect of benzydamine on the respiratory burst of phagocytic cells

Cell type	Metabolite measured and stimulant	Benzydamine concentration	Effect	Reference
Human monocytes and macrophages	H_2O_2			
	Zymosan stimulation	100 μmol/L	50% inhibition	[44]
	PMA stimulation	100 μmol/L	No effect	[44]
Human neutrophils	Superoxide			
	PMA stimulation	30 μmol/L	No effect	[44]
	fMLP stimulation	30 μmol/L	25% inhibition	[44]
Guinea pig macrophages	Superoxide	300 μmol/L	50% inhibition	[47]
Mouse neutrophils	Superoxide lucigenin-dependent chemiluminescence	17 μmol/L	50% inhibition	[34,46]
Mouse neutrophils	H_2O_2/HOCl luminol-dependent chemiluminescence	100 μmol/L	50% inhibition	[46]

MEMBRANE STABILIZATION

Benzydamine appears to possess a generalized membrane-stabilization effect. This effect is shown by a variety of actions of benzydamine. A membrane-stabilizing effect of benzydamine is supported by its similar activities in some systems to those of well-recognized membrane stabilizers.

(a) Benzydamine has a local anaesthetic effect on the rabbit eye [48]. When studied in healthy human volunteers, 4 mmol/L benzydamine mouthwash solution produced a local anaesthetic effect for 90 min and was claimed to depress swallowing, an effect consistent with local anaesthetic activity [49].

From admittedly limited information, benzydamine does not appear to be simply a local anaesthetic. Thus, benzydamine decreases the hyperalgesia produced by pressure on an inflamed paw of the rat to a much greater extent than the pain produced by pressure on a normal paw [50]. This is an indicator of anti-inflammatory activity. Local anaesthetics, in contrast to benzydamine, have little or no anti-inflammatory activity [51,52].

(b) At concentrations of 10–100 μmol/L, levels obtained in oral tissue, benzydamine stabilizes hepatic lysosomal membranes [53]. At 3–30 μmol/L, benzydamine also inhibits the release of specific and azurophil granules from neutrophils [44].

(c) Like benzydamine, other membrane stabilizers, such as β-blockers in high concentrations and local anaesthetics inhibit the oxidative burst of human neutrophils [54,55].

(d) Again like benzydamine, several acidic NSAIDs inhibit both the degranulation and the oxidative burst of neutrophils [56,57]. The acidic NSAIDs have been suggested to be membrane stabilizers although the concentrations required to produce these effects are probably too high to be related to their in-vivo activity.

(e) The non-specific action on blood vessels (section on Anti-inflammatory effects in experimental animals, above) may be due to stabilization of cell membranes.

(f) The inhibition of the release of inflammatory mediators from cells is consistent with a membrane-stabilizing effect (section on Effect on inflammatory cells).

(g) The cellular uptake of actinomycin D, an antiblastic drug, is enhanced in the presence of benzydamine. Other transport systems, such as those for glucose and amino acids, were unaffected, indicating that benzydamine does not contribute to generalized increased permeability of the membrane [14].

(h) Benzydamine potentiates the formation of cyclic 3′,5′-AMP by isolated fat cells [42]. This effect is suggested to be the result of the local anaesthetic activity of the drug affecting cation movement within the cell.

These various actions of benzydamine and other drugs are suggestive of benzydamine possessing the general property of stabilization of membranes in addition to other more selective actions. We suggest that benzydamine may be able to inhibit neurogenic inflammation in particular. Inhibition of the release of inflammatory mediators, such as substance P and calcitonin gene related peptide (CGRP), from sensory nerve endings is a feasible explanation for the local anti-inflammatory activity of benzydamine. Substance P can cause the release of histamine from mast cells and any inhibition of histamine release could contribute to the anti-inflammatory activity of benzydamine. Benzydamine inhibits the release of granules from neutrophils, an effect which may further contribute to the anti-inflammatory effects of the drug. The local anaesthetic activity of benzydamine may also contribute to inhibition of neurogenic inflammation. Further work on its membrane-stabilizing effects is required to test these speculations.

CONCLUSIONS

Benzydamine has pharmacological effects which are quite dissimilar to other non-steroidal anti-inflammatory drugs. In particular, benzydamine has little or no effect on the synthesis of prostanoids. The mechanism of the anti-inflammatory activity of benzydamine is unclear but may be due to its membrane-stabilizing effect or to inhibition of the synthesis of TNF-α. The antibacterial property of benzydamine may assist its anti-inflammatory activity when applied to the mouth. Knowledge of the concentrations of the drug in tissues is required to determine whether effects seen in vitro are relevant to its therapeutic actions.

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