PRESCRIBING INFORMATION

PrTANTUM™
Benzydamine Mouthwash, BP
Benzydamine Hydrochloride
1.5 mg/mL (0.15% w/v)

Oral Rinse
Local Analgesic

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

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Control #: 256416

NAME OF DRUG

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1.5 mg/mL (0.15% w/v)

ACTION

Animal studies using the parenteral route have shown that TANTUM (benzydamine hydrochloride) possesses properties of an analgesic-anti-inflammatory agent. This effect is not mediated through the pituitary-adrenal axis. Studies using the topical route have demonstrated the local analgesic properties of benzydamine hydrochloride. In controlled studies in humans with oro- pharyngeal mucositis due to radiation therapy, TANTUM Oral Rinse provided relief through reduction of pain and edema. Similar studies in patients with acute sore throat demonstrated relief from pain.

Benzydamine HCl has been detected in blood and urine after gargling four times for 20 seconds, in rapid succession, each time with a volume equivalent to 25.5 mg benzydamine per 70 kg body weight (approximately 17 ml per gargle). The average maximum plasma level of 59 ng/ml (range 17 to 173) was obtained 2 hours after ingestion. Benzydamine was still detectable 24 hours later in 7 out of 10 subjects after gargling (average plasma level of 7 ng/ml) and in 9 out of 10 subjects after ingestion (average 32 ng/ml).

The urinary excretion was completed within 3-4 days after the single dose in both groups; about 46% of the dose was recovered in gurglers, and 26% in ingestors. Repeated administration for 7 days did not result in a significant accumulation of benzydamine in plasma.

INDICATIONS

TANTUM Oral Rinse (benzydamine HCl) is indicated for the relief of pain in acute sore throat and for the symptomatic relief of oro-pharyngeal mucositis caused by radiation therapy.

CONTRAINDICATIONS

TANTUM (benzydamine HCl) is contraindicated in subjects with a history of hypersensitivity to benzydamine hydrochloride or any of its excipients.

PRECAUTIONS

The use of undiluted TANTUM (benzydamine HCl) may produce local irritation manifested by burning sensation in patients with mucosal defects. If necessary, it may be diluted (1:1) with lukewarm water.

Since TANTUM (benzydamine HCl) is absorbed from the oral mucosa and excreted mostly unchanged in the urine, a possibility of its systemic action has to be considered in patients with renal impairment.

TANTUN contains methylparaben and propylparaben. They are known to be associated with hypersensitivity in single or repeated uses.

Use in Pregnancy
The safety of benzydamine HCl has not been established in pregnant patients. Risk to benefit ratio should be established if TANTUM Oral Rinse is to be used in these patients.

Use in Children
Safety and dose directions have not been established for children five years of age and younger.

ADVERSE REACTIONS

The most frequent adverse reactions reported are local numbness (9.7%), local burning or stinging sensation (8.2%), nausea and/or vomiting (2.1%).

The least frequent were reports of throat irritation, cough, dryness of the mouth associated with thirst, drowsiness, headache, bronchospasm, and hypersensitive reactions, including anaphylactic and anaphylactoid reactions.

TREATMENT OF OVERDOSE

Both intentional and accidental overdoses have been reported with benzydamine HCl gargle. In oral doses much larger than those recommended, the symptoms of acute overdose of benzydamine hydrochloride were observed. The symptoms include (but are not limited to) seizures (convulsions), excitation, sweating, loss of full control of bodily movements (ataxia), trembling (tremor) and vomiting. After massive oral overdose (500-3,000 mg per day), visual hallucinations, sickness (nausea), vomiting, irritation of the gullet, anxiety or nervous excitement (agitation), headache, and irritability were reported and are common signs of benzydamine misuse or recreational use.

Since no specific antidote for benzydamine is available, cases of overdoses of the formulation should receive supportive, symptomatic treatment aimed at rapid elimination of the drug.

For management of a suspected drug overdose, contact your regional poison control centre.

DOSAGE AND ADMINISTRATION

Not less than 15 ml of the liquid should be used for each gargle or rinse and repeated three or four times a day, depending on the severity of the treated condition. The liquid should be kept in contact with the inflamed mucosa for at least 30 seconds and then expelled from the mouth. Administration should begin the day prior to commencement of radiation therapy and continue daily during the treatment period as well as after cessation of radiation applications until the desired improvement is obtained.

In acute sore throat, gargle with 15 ml every 1 ½ to 3 hours. The solution should be expelled from the mouth after use.

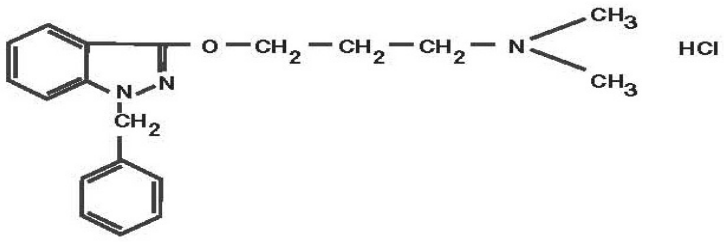
AVAILABILITY

TANTUM (benzydamine HCl) Oral Rinse is available in 100- and 250-mL bottles. TANTUM is a clear yellow-green liquid containing 0.15% Benzydamine Hydrochloride, Methylparaben and Propylparaben as preservatives in a solvent consisting of Water, Glycerin and Ethanol.

CHEMISTRY

Benzydamine Hydrochloride

Chemical Name: 1-benzyl-3-(3-(dimethylamino)-propoxy)-1H-indazole monohydrochloride



Molecular Formula: $C_{19}H_{23}N_3O.HCl$

Molecular Weight: 345.86 g/mol

Physicochemical Properties

Description: White, odorless, crystalline powder.

Solubility: Soluble in water (10% w/v), ethanol, methanol and chloroform, sparingly soluble in ether and petroleum ether.

PHARMACOLOGY

Parenteral benzydamine HCl in animal experiments inhibited morphologies indicative of pain due to various experimental inflammations (produced by carrageenin, serotonin, histamine, yeast, kaolin, dextran, egg albumin, cotton-pellet, croton oil granuloma and acrolein inhalation). It had relatively little or no effect on Freund's adjuvant arthritis and on erythema produced by UV radiation or X-rays.

The analgesic activity of benzydamine was more pronounced in models involving experimental inflammation than in non-inflammatory pain.

The mechanism of anti-inflammatory action is not related to a stimulation of the pituitary- adrenal axis. Like other non-steroidal anti-inflammatory agents benzydamine inhibits the biosynthesis of prostaglandins under certain conditions, but its properties in this respect have not been fully elucidated.

Benzydamine hydrochloride possesses a local analgesic activity at low concentrations (0.15% - 1.0%) as demonstrated by corneal reflex inhibition in rabbits or in human volunteers using benzydamine mouthwash.

Peripheral reflexes were transiently inhibited after i.v. administration to cats.

PHARMACOKINETICS

Plasma concentrations of benzydamine were measured following the use of TANTUM ORAL RINSE as a gargle-mouthwash.

Three groups of fasted healthy volunteers completed a randomized cross-over study in which either a dose of 25.5 mg/70 kg body weight was ingested or was used as a mouth rinse and gargle. After 20 seconds the solution was expectorated. This procedure was repeated four times in succession. Based on the difference in the total quantity used and that expectorated indicated that the total quantity absorbed was 9.67 mg/70 kg.

Figure 1 shows the plasma concentration-time curves. As would be expected from the difference in the quantities ingested between the swallow and gargle treatments, the amount absorbed differed significantly.

When the dose ingested during gargling is normalized for dose, no difference was observed in the total amount of benzydamine absorbed.

In another study, subjects were administered the same total dose divided in four equal doses at 5-hour intervals for 7 days. The amount ingested by swallowing was 6.38/70 kg four times daily and by gargling 2.69 mg/70 kg 4 times daily. Blood samples were taken 3 hours after the third dose and 24 hours after the first dose each day. The results are given in Figure 2. The differences seen are due to dose differences but indicate that a steady-state level is reached within 1-2 days of treatment and no accumulation of benzydamine occurs. Peak benzydamine concentrations of 30 -40 ng/ml were low when given as a gargle.

Figure 1: Time course of plasma concentrations in man after administration of benzydamine as mouthwash in relation to oral administration of liquid form used for mouthwash

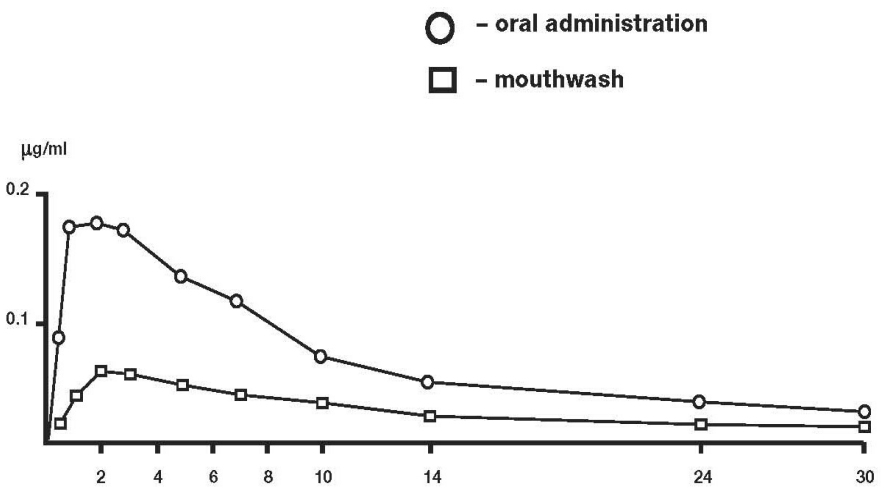


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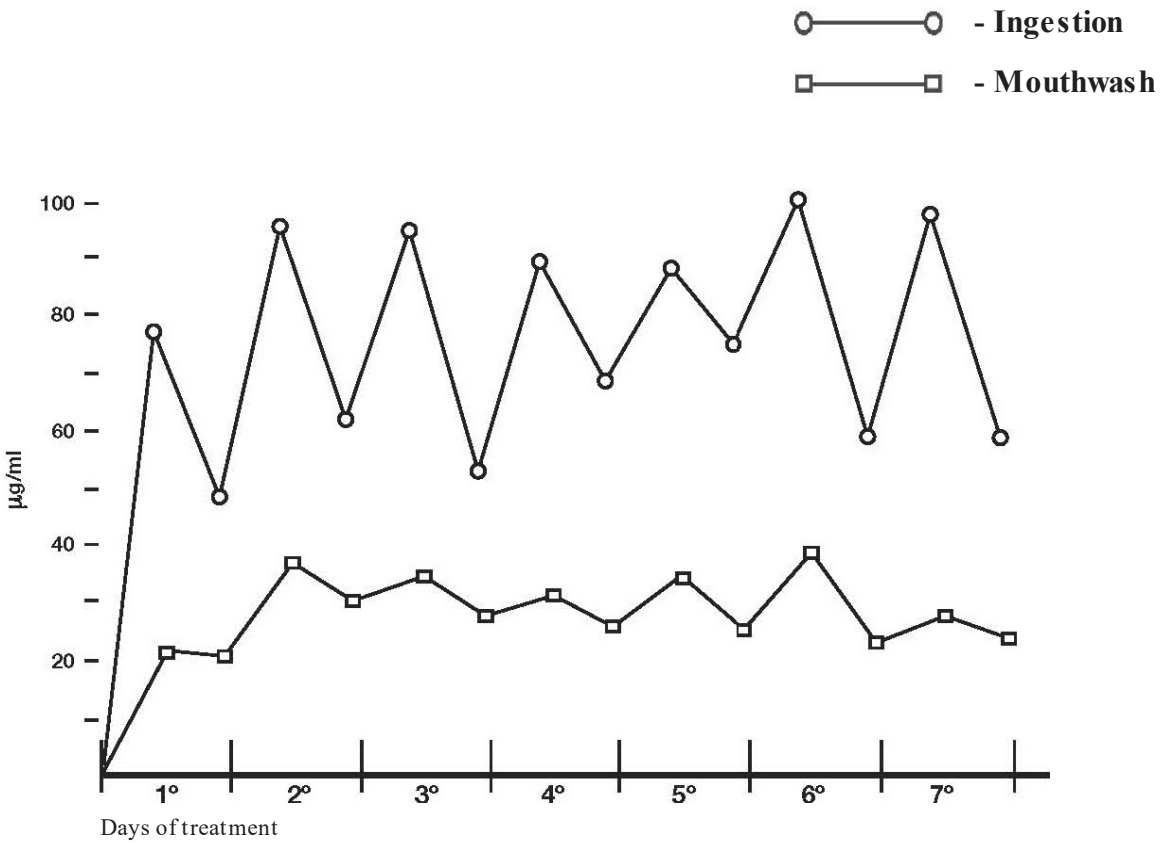
Figure 2: Plasma benzydamine levels during repeated administrations



TOXICOLOGY

Acute Toxicity

LD_{50} (mg/kg)

ROUTE	MOUSE	RAT	RABBIT	CAT	DOG	HORSE
i.v.	33	-	-	22	29	23
i.p.	110	100	-	-	-	-
s.c.	218	-	-	-	-	-
p.o.	515	1050	400	-	-	-

Acute toxic effects in mice and rats include muscle relaxation, ataxia and, at lethal dose, prostration and chronic convulsions.

Subacute Toxicity

Benzydamine was administered to rats (Long-Evans) at daily oral doses of 200 mg/kg for 1 month, at increasing doses from 200 to 300 mg/kg over 1 month or from 250 to 500 mg/kg over 3 months or admixed in the diet (0.5% for 3 months; 0.01% and 0.1% for 6 months). Liver enlargement and a decrease in the growth rate were observed in rats treated with doses of 300 – 500 mg/kg/day or fed with the 0.5% diet. No histological changers were found in liver or other organs. Seven out of 30 rats died within 5 days after the daily dose was increased from 250 to 500 mg/kg.

Mice (CF-1) were given a diet containing 0.01% or 0.1% benzydamine for 6 months (approximately 15 and 150 mg/kg). The mice exhibited an increase in liver weight, without histological changes, at the higher concentration. No other pathological alterations were noted.

Dogs were treated with benzydamine 30 mg/kg p.o. for 1 or 6 months. Increasing the daily dose to 45 mg/kg induced vomiting. No changes in behavior, growth, organ weights, histology, blood counts, urinalysis, SGOT, glucose, BUN, serum electrophoresis and osmotic resistance RBC were seen.

Topical administration as a 5% gel to rat and rabbit skin for 30 days did not result in any systemic toxicity.

Chronic Toxicity

Rats (Charles River) were treated daily with oral doses of 0, 10, 50, and 250 mg/kg for 18 months; urinalysis, hematological tests and determinations of fasting blood sugar, BUN, SGOT, SGPT, prothrombin time and coagulation time were performed and found to be within normal limits. High dose females showed hyperactivity. High dose animals showed inhibited growth rate. There was an increased liver/body weight ratio in males of the highest dosage group. Biochemical and hematological tests yielded normal values. A 12-month experiment in Rhesus monkeys treated with daily doses of 0,7,20 and 60 mg/kg by gavage (10 animals per dose) revealed no pathological alterations in the biochemical and hematological tests performed.

Two animals died after receiving a single dose of 120 mg/kg, while two others were sacrificed in moribund condition after receiving 60 mg/kg per day after three and one-half and thirty-two days, respectively.

Local Tolerance

Rats appeared to be sensitive to skin applications of 5% benzydamine HCl gel for 30 days at 0.5 and 1 gm/day. No appreciable irritation was seen on normal or abraded skin of rabbits after application of the same gel for 30 days, or 5% cream for 1 day. Cats, dogs and ponies received a 2-week application of 5% cream to shaved skin without signs of intolerance.

Subcutaneous injections in rats and conjunctival installations in rabbits produced transient symptoms of irritation after use at concentrations of 0.25% and higher.

No sensitization could be demonstrated after repeated intradermal injections (0.1%) to guinea pigs.

Reproduction Studies

Orally administered benzydamine HCl did not increase the incidence of fetal malformations in mice, rats and rabbits. Non-specific skeletal anomalies and retarded ossification were reported in the offspring of mice treated with 100 mg/kg/day s.c. or 240 mg/kg/day p.o. The incidence of dead fetuses was increased in rats, particularly at higher doses (200 and 240 mg/kg/day p.o.) These findings were accompanied by lower maternal weights in the high dosage groups and were considered as manifestations of maternal toxicity rather than as a specific teratogenic effect on fetal development.

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