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3,499,087

METHOD FOR TREATING ULCERS WITH BENZOYL ESTERS OF 2-TERTIARY AMINO-1-PHENYL ETHANOLS

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No Drawing. Filed May 2, 1967, Ser. No. 635,340
Int. Cl. A01n 9/24

U.S. Cl. 424—308

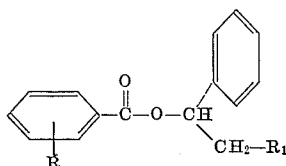
2 Claims

ABSTRACT OF THE DISCLOSURE

Compositions containing benzoyl esters of 2-tertiary-amino-1-phenyl ethanol as either the free base or acid addition salts are valuable for the treatment of ulcers. 2-diethylamino-1-phenylethyl benzoate is the preferred compound.

This invention relates to compositions for the treatment of ulcers and to a method of treating ulcers. In particular it relates to compositions comprising benzoyl esters of 2-tertiary amino-1-phenyl-ethanols and the uses of said compositions in the treatment of ulcers.

The benzoyl esters of the 2-tertiary-amino-1-phenyl-ethanols have the structure



wherein R is hydrogen or lower alkoxy, such as methoxy or ethoxy, and R₁ is a secondary amino group such as pyrrolidyl, piperidyl, morphyl, dimethylamino, diethylamino, methylethylamino, and the like, and are described in J. Am. Chem. Soc. 81, 203 (1959). Typical benzoyl esters of the compositions of this invention are:

Compound:	No.
2-diethylamino-1-phenylethyl benzoate	A
2-pyrrolidino-1-phenylethyl benzoate	B
2-diethylamino-1-phenylethyl 2-methoxybenzoate	C
2-diethylamino-1-phenylethyl 2-ethoxybenzoate	D
2-diethylamino-1-phenylethyl 4-ethoxybenzoate	E

The esters are preferably used in the form of their pharmaceutically acceptable non-toxic acid addition salts such as the hydrochloride, hydrobromide, phosphate, sulfate, acetate, lactate, malate, succinate, maleate, malonate, gluconic, glucuronate, benzoate, silicylate, cinnamate, mandelate, nicotinate, and the like.

The benzoyl esters of the compositions of this invention also possess topical anesthetic activity approximating that of procaine and lidocaine. Bayer, Zentralbl. f. Inn. Med. 55, 577 (1934), unexpectedly found that ulcer patients given a 0.25% solution of procaine, a topical anesthetic, orally to facilitate the passage of contrast media through the pylorus for radiography showed remarkable objective and subjective improvement. He assumed that procaine had a specific action on the healing of the lesions and in this connection leaned towards the idea that local anesthesia of a lesion or a focus of inflammation resulted in more rapid healing.

A considerable literature has since accumulated and was reviewed in part by Lunderquist, Svenska Lakartidn 58, 15 (1961). Despite the experience of many investigators with local anesthetics, their use for the relief of gastro-

2

intestinal discomfort has generally been ignored. The various clinical reports detailing the complicated methods for administration, lack of potency, inadequate duration of action, toxicity, adverse side effects have contributed to much of the lack in enthusiasm. Moreover, absence of agreement among laboratory and clinical workers has made this an area of controversy.

One of the most recent additions to therapy is oxethazaine. This is an extremely powerful local anesthetic. It is unusual in that it is a weak base relatively little dissociated at gastric pH. However, Balmforth et al., Br. Med. J. 1, 355 (1964), showed that oxethazaine did not improve the capacity of an aluminum-magnesium hydroxide mixture to relieve pain associated with duodenal ulcer. There is good reason to suspect that the action of oxethazaine is purely a surface anesthesia phenomenon. Its pain relieving potential is dependent upon direct action on nerve endings at the diseased site. Its potent spasmolytic action occurs only upon direct contact with the intestine; parenteral administration fails to alter contractility or tone of intestinal segments in dogs. It is, therefore, unlikely that oxethazaine acts indirectly through a neuronal circuit.

The clinical failures reported for procaine, lidocaine and other topical agents against ulcer pain, hypermotility, and gastric hyperacidity is attributable to the fact that they do not exist in sufficiently undissociated form (free base) at gastric pH to be effective. Where clinical effectiveness has been reported, the anesthetics were administered by perfusion of the mucosa or on the ulcer crater; the direct contact permitted the topical action to occur before the acidity of the stomach decreased the amount of available free base. Further, presentation of anesthetic, by drip, provided a continuous supply of free base for topical action on the target site.

I have found that the benzoyl esters of the 2-tertiary-amino-1-phenyl-ethanols, particularly the benzoyl ester of 2-diethylamino-1-phenyl-ethanol, used in the compositions of this invention have properties which make them more effective and useful in the treatment of ulcers as compared to other topical anesthetics. The esters of the compositions of this invention surprisingly are relatively undissociated at an acid pH so that significant amounts of free base are available to penetrate the lipid sheath of nerves to affect anesthesia. This weak basicity probably enhances the potency of the compounds in the acidic medium of the stomach.

The esters have a mild relaxing effect on the intestinal musculature. Since various gastric and intestinal disturbances frequently produce hypermotility, possibly as a result of inflammation, this property is a distinct asset. Compound A also possesses mild tranquilizing action.

In addition, the esters possess anti-inflammatory activity, particularly in reducing inflammation resulting from chronic irritation as shown by the inhibition of granuloma formation around cotton pellets according to the technique of Meier et al., Experientia 6, 469 (1950), as modified by Winter et al., J. Am. Pharm. Assoc. (Sci. ed.) 46, 515 (1957). Table I shows the antigranuloma potency of compound A as compared to other anti-inflammatory agents.

TABLE I.—ANTIGRANULOMA POTENCY

Rank		Approx. ED ₂₀ (mg base/kg.)
I	Dexamethasone	0.3
II	Indomethacin	0.5
III	Compound A	2.5
IV	Hydrocortisone	15.0
V	Phenylbutazone	20.0

Although dexamethasone and indomethacin are approximately 5–8 times more potent than compound A, the

latter is significantly better than either hydrocortisone and phenylbutazone. For equivalent antigranuloma action, compound A appears to exceed the potency of either hydrocortisone or phenylbutazone by factors of 6 and 8. These findings are of particular interest since the favorable potency of these esters in reducing inflammation resulting from chronic inflammation makes them more valuable in their use in anti-ulcer therapy.

The esters also alter gastric secretion and acidity.

Using both the "Chay" rat and restrained rat techniques, the modification of ulcer formation by the benzoyl esters of 2-tertiary amino-1-phenyl-ethanols has been demonstrated.

TABLE II.—INHIBITION OF ULCER FORMATION—"SHAY" RAT

Compd. Admn.	Dose (mg. base/kg.)	No. used	Survival ¹ (percent)	Mean type ulceration
Saline.....		35	91.4	3.1±0.3
Atropine.....	0.5	12	100.0	1.0±0.5
	1.0	12	100.0	1.4±0.5
	2.0	12	100.0	1.4±0.5
	4.0	12	100.0	0.6±0.3
	8.0	10	100.0	0.0±0.0
Oxethazaine.....	0.2	15	93.3	3.4±0.5
Compound B.....	1.0	26	96.2	1.7±0.4
Compound A.....	1.0	15	100.0	1.6±0.4

¹ Based on number surviving surgery and series of 3 injections.

² Grading system: 0=normal stomach. 1=ten or less small ulcers, 1-3 mm. diameter; 2=eleven or more small ulcers, 1-3 mm. diameter; 3=one or more ulcers, 4-6 mm. diameter; 4=one or more ulcers, 7+ mm. diameter; 5=one or more perforations of wall.

Table II shows that parenteral administrations of atropine and compositions containing compounds A and B afford statistically significant degrees of protection against ruminal ulcer formation. 1.0 mg. base/kg. compound B and 1.0 mg. base/kg. compound A are about as effective as 1.0-2.0 mg. base/kg. atropine, an anti-cholinergic agent. Oxethazaine has no inhibitory potential when administered at the established human therapeutic dose level.

These above studies have also indicated that administration of the compositions of this invention orally or parenterally reduced the gastric secretion. The latter effect of these compositions were also shown on tests with chronic pouch dogs. Therefore, it would appear that the effect of the compositions proceed through a local mechanism and other mechanisms, possibly by central action.

The benzoyl esters of 2-tertiary-amino-1-phenylethanols are administered internally, either parenterally or orally in the solid form of tablets or capsules or in solution.

In accordance with the invention there are provided compositions for the treatment of ulcers and methods of treating ulcers using said compositions. This will appear more fully from the examples which follow, which are set forth by way of illustration only, and it is intended to cover all changes and modifications of examples herein which do not constitute departures from the spirit and scope of the invention. The examples illustrate various types of compositions coming within the invention for a variety of administration techniques.

EXAMPLE I

A composition of matter for oral administration, comprising the hydrochloride of 2-diethylamino-1-phenylethyl benzoate as the active ingredient in combination with a suitable carrier, was prepared by thoroughly mixing together 300 grams of the active compound and 3500 grams of betalactose (milk sugar), passing the blended mixture through a No. 40 screen and filling the mix into gelatin capsules, 450 mg. per capsule, each capsule to contain 100 mg. of active ingredient.

EXAMPLE II

A composition of matter for oral administration, in tablet form, comprising the hydrochloride of 2-diethylamino-1-phenylethyl benzoate as the active ingredient in

combination with a suitable carrier, was prepared by compounding the following ingredients into a tablet mix:

	Grams
Active ingredient	308
Sugar	308
Lactose	177
Dextrin	50
Starch	98
Talcum	10
Stearic acid	10
Starch paste, q.s. to make 1000.	

The above mix was compressed into tablets, weighing approximately 325 mg. each tablet containing 100 mg. of active ingredient.

EXAMPLE III

A composition of matter for parenteral administration comprising the hydrochloride of 2-diethylamino-1-phenylethyl benzoate as the active ingredient in combination with a liquid carrier and having the following formula was prepared:

	Grams
Active ingredient	25
Benzyl alcohol	5
Water, pyrogen-free, q.s. to 500 ml.	

In making this solution the active ingredient was dissolved in 400 ml. of pyrogen-free water, the benzyl alcohol added, and the solution was made up q.s. to 500 ml.; after which the solution was filtered aseptically and filled aseptically in ampule containing 1 ml., under a nitrogen atmosphere. The resulting solution supplied a dosage unit of 50 mg. of active ingredient.

EXAMPLE IV

A liquid composition of matter for oral administration comprising 2 - pyrrolidino-1-phenylethyl benzoate as the active ingredient in combination with a liquid carrier and having the following formula was prepared:

	Grams
Active ingredient	25
Benzoic acid	10
Liquid sugar	35
Cherry flavor	5

Water q.s. to give a solution containing about 30 mg. of active ingredient per teaspoon.

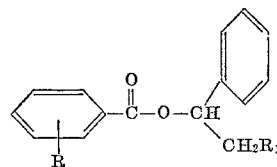
Compositions made to contain from 5 mg. to 100 mg. per dosage unit may be similarly prepared.

Compositions of matter similar to those in Examples I and II may be made to include other substances having therapeutic properties useful in the treatment of ulcers, such as pharmaceutically acceptable antacids as aluminum hydroxide, magnesium trisilicate, calcium carbonate, and the like.

In the treatment of ulcers the benzoyl esters of the 2-tertiary-amino - 1-phenyl-ethanols are administered internally, either parenterally or orally in the solid form of tablets or capsules or in solution, in single or divided doses in a range of about 1 to 10 mg./kg. daily.

I claim:

1. A process for the treatment of ulcers which comprises administering to a host suffering from ulcers a therapeutically effective amount of a composition in dosage unit form comprising 5 to 100 mg. of a compound selected from the group consisting of a compound of the structure



wherein R is hydrogen or lower alkoxy and R₁ is pyrrolidyl, piperidyl, morphyl, diethylamino, or dimethylamino, and their pharmaceutically acceptable, non-toxic acid addition salts, admixed with a suitable pharmaceutical carrier at a daily dose of from about 1 to 10 mg. of compounds per kg. of body weight of said host.

2. A process according to claim 1, wherein the compound is 2-diethylamino-1-phenylethyl benzoate.

References Cited

Shapiro et al., J. Am. Chem. Soc. 81, pp. 203-211 (1959).

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U.S. Cl. X.R.

424—308, 274, 267