PHENYLEPHRINE PRODRUG USEFUL AS MYDRIATIC AGENT

Inventors: Ronald D. Schoenwald; Du-Shieng Chien, both of Iowa City, Iowa

Assignee: University of Iowa Research Foundation, Iowa City, Iowa

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Primary Examiner—Donald G. Daus
Assistant Examiner—Cecilia Shen
Attorney, Agent, or Firm—Zarley McKee, Thomte, Voorhees & Sease

ABSTRACT
An oxazolidine derivative of phenylephrine, and the non-toxic pharmaceutically acceptable salt forms thereof. The prodrug is much quicker absorbed across the cornea of the eye, does not induce the same unwanted side effects as phenylephrine, and can produce the same mydriatic effect as phenylephrine at dosage levels of approximately one-tenth the level of phenylephrine.

12 Claims, 2 Drawing Figures
PUPILARY DILATION STUDY

- PRODRUG (OXAZOLIDINE DERIV.) (10 µL)
- PHENYLEPHRINE HCL (10 µL)

PUPILARY DIAMETERS (mm)

MINUTES AFTER ADMINISTRATION

Fig. 1

1% PRODRUG VS. 10% VISCOUS PE HCL

- 1% OXAZOLIDINE PRODRUG (10 µL)
- 10% VISCOUS PHENYLEPHRINE HCL (10 µL)

PUPILARY DIAMETERS (mm)

MINUTES AFTER ADMINISTRATION

Fig. 2
PHENYLEPHRINE PRODRUG USEFUL AS MYDRIATIC AGENT

BACKGROUND OF THE INVENTION

The present invention relates to a novel and therapeutically oxazolidine derivative of 3-hydroxy-alpha-(methylamino)methyl)-benzyl alcohol, commonly known as phenylephrine, and to pharmaceutical compositions containing the same.

Phenylephrine is a well-known pharmaceutically active amine whose principal use in the field of ophthalmology is as a mydriatic. There are, however, certain known disadvantages associated with the use of phenylephrine as a mydriatic agent. Those disadvantages have limited the use of this highly effective drug. Thus, in spite of the fact that it is one of the most effective mydriatics available, its use is significantly limited because of the significant side effects which may occur in some individuals treated with phenylephrine. Those unwanted significant side effects range from hypertension, syncope, and even in some cases to myocardial infarction, leading to death. Such side effects have been reported with doses of topical ocular phenylephrine.

One approach which has been used from time to time in the past is the effort to develop successful prodrugs of phenylephrine. As those skilled in the art know, the term prodrug refers to a therapeutic agent that requires enzymatic transformation to demonstrate therapeutic activity. In other words, the prodrug itself is not therapeutically active, but once subjected to enzymatic activity by the host organism it is converted to an active drug. In the past there have been some attempts to make prodrugs of phenylephrine, with varying degrees of success. For example, Mindel et al., "Is Phenylephrine Pivlante a Prodrug?", Arch. Ophthalmol. 96, 2220 (1980) suggests the reaction product of phenylephrine and pivalic acid to provide a pivalic acid ester as a possible prodrug. However, as reported in that article, phenylephrine pivolate itself produces these side effects. And, it goes without saying that to have a successful prodrug, the prodrug itself must not produce the unwanted side effects, even though it may be effectively converted within the body to the active drug. Johansen et al., "Prodrugs as Drug Delivery Systems XXV: Hydrolysis of Oxazolidines—A Potential New Prodrug Type", Journal Pharm. Sci., 72, 1294 (1983) discloses some prodrug possibilities of ephephedrine. However, ephephedrine is not commonly used ophthalmically and is biologically different in activity than phenylephrine, with ephephedrine being used orally for narcolepsy, bronchial asthma and nasal congestion. In contrast, the oxazolidine derivative of phenylephrine increases the bulk considerably on the amine function, the latter of which is responsible for phenylephrine's activity. With the addition of oxazolidine to the amine function, the prodrug would be expected to be devoid of alpha-adrenergic activity (A. Burger, "Medicinal Chemistry", 3rd ed., Wiley-Interscience, 1970, p. 1248).

Accordingly, there is a continuing and real need for safe and effective prodrugs of phenylephrine.

This invention has as its primary objective the development of a novel and useful oxazolidine derivative of phenylephrine, which when used at mydriatically effective levels does not produce side effects similar to phenylephrine, and at the same time is more quickly absorbed across the cornea than phenylephrine.

Another objective of the present invention is to provide a safe and pharmaceutically effective mydriatic which is a prodrug of phenylephrine, prepared from reacting phenylephrine with pivaldehyde.

Yet another objective of the present invention is to prepare mydriatic compositions for topical ocular treatment, useful in ophthalmic diagnosis and surgery.

Another objective of the present invention is to provide the compound in a suitable non-aqueous vehicle that possesses increased stability and that can be administered in pharmaceutical formulations to produce a local or systemic physiological effect.

A further objective of the present invention is to provide a method of preparing a prodrug of phenylephrine which comprises reacting phenylephrine with pivaldehyde to produce a product which is stable in oil suspensions but which reverts to phenylephrine upon hydrolysis upon contact with tears.

The method and manner of accomplishing these and other objectives of the invention will become apparent from the detailed description which will follow hereinafter.

SUMMARY OF THE INVENTION

This invention relates to a novel compound which is a prodrug of phenylephrine useful as a mydriatic agent. The prodrug is an oxazolidine derivative of phenylephrine and in its preferred form constitutes 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine. The prodrug is prepared by reacting phenylephrine with pivaldehyde. The reaction product is suspended in an non-toxic non-eye-irritating oil suspension in the preferred form, resulting in a mydriatic composition which does not have the typical side effects of phenylephrine, but at the same time is equally as effective at producing pupil dilation. It is mostly quickly absorbed across the cornea than phenylephrine and as a result can be used at dosages at levels down to one-tenth the amount of phenylephrine.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a pupillary dilation study for the prodrug of this invention in comparison with phenylephrine itself, with both at equal dose levels.

FIG. 2 shows a comparison of pupillary diameters for phenylephrine with the prodrug of this invention, with the prodrug at 1/10 the dose level of phenylephrine.

DETAILED DESCRIPTION OF THE INVENTION

One successfully obtains the objects of the present invention by employing as a mydriatic, a compound of the formula:

or the non-toxic pharmaceutically acceptable salt forms thereof.

This compound can also be conveniently named 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine. Both the compound itself in its base form, or its pharmaceutically acceptable non-toxic acid salts thereof can be used. Such acid salt forms of biologically active com-
pounds which are non-toxic are well-known and within the
skill of the art. For example, such non-toxic salts
include those derived from inorganic acids such as hy-
drochloric, hydrobromic, sulfuric, sulfamic, phos-
phoric, nitric, and the like; and the salts prepared from
organic acids such as acetate, propionate, succinate, glycolic,
stearic, lactic, malic, tartaric, citric, ascorbic, pamoic,
maleic, benzoic, glutamic and salicylic.

Such pharmaceutically accepted salts of the base
form of the compound depicted in the previously pre-
vented formula can be synthesized by conventional,
chemical methods. Generally, the salts are prepared by
reacting the free base form with stoichiometric amounts
or with an excess thereof of the desired salt forming
inorganic or organic acid, in a suitable solvent, or vari-
obious combinations of solvents. For example the free base
can be dissolved in a mixed aqueous solution of the
appropriate acid and the salt recovered by standard
techniques, like for example, by evaporation of the
solution.

Generally it has been found that the prodrug of this
invention is not particularly stable in aqueous solutions.
Therefore, effective pharmaceutical compositions in-
clude the prodrug in an oil suspension, which may be a
mineral oil or an edible vegetable oil. Preferred oil
suspections include the usual triglyceride vegetable
oils or preferably ethyl alcohol or other acceptable solvents
such as sesame seed oil, cottonseed oil, soybean oil, coconut oil, rapeseed oil,
peanut oil, olive oil, palm oil, palm kernel oil, corn oil,
caster oil, sunflower seed oil, wallflower oil, and pil-
chard oil.

The dosage of prodrug in the mydriatic composition
of the present invention can comprise from about 0.25%
by weight of the composition up to about 10% by
weight of the composition which is to be topically ap-
plied to the eye. Preferably the composition is from
about 0.5% by weight of the prodrug up to about 5% by
weight of the prodrug. The balance of the composition
is primarily the oil. The preferred oil is sesame seed oil.

The pharmaceutical composition, besides the pre-
ferred vegetable oil carrier may contain other non-toxic
auxiliary substances such as anti-bacterial, anti-fungals,
anti-oxidants, wetting agents, preservatives and the like.
Examples include polyethylene glycols 200, 300, 400
and 600, carbowaxes 1,000, 1,500, 4,000, and 10,000;
bacterial components such as quaternary ammonium
compounds, phenylmercuric salts known to have cold
sterilizing properties and which are noninjurious in use,
thimerosal, propyl paraben, buffering ingredients such
as sodium chloride, sodium borate, sodium acetate,
gluconate buffers, and other conventional ingredients
such as sorbitan monolaurate, triethanolamine oleate,
polyoxyethylene sorbitan monopalmitate, dioctyl so-
da sulfosuccinate, monothioglycerol, thiosorbitol,
ethylenediamine tetracetic acid, and the like.

An example of a typical pharmaceutical composition
to be used with the compound 2,4-buty1-3-methyl-5-(m-
hydroxyphenyl)-1,3-oxazolidine in its base form, in-
cludes the following:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorobutanol</td>
<td>0.25</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.05</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>0.01</td>
</tr>
<tr>
<td>Water, Agent, Phenolene P-103</td>
<td>0.05</td>
</tr>
<tr>
<td>Alpha Tocopherol</td>
<td>0.05</td>
</tr>
<tr>
<td>BHT</td>
<td>0.03</td>
</tr>
<tr>
<td>BHA</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Surprisingly, and it is not known precisely why, the
prodrug of the present invention forms a side ring, tying
up the amine group of the basic phenylephrine struc-
ture, but still upon enzymatic hydrolysis becomes bio-
logically active. Previously it has been believed that if
the amine group were sterically interfered with, there
would be no mydriatic activity. Moreover, other pro-
drugs of phenylephrine which have been prepared in
the past themselves had undesirable myocardial side
effects. The present ones do not. Moreover, as will be
demonstrated in the example, the present compounds
are as effective as phenylephrine, at concentrations as
low as 10% of that normally used in dosing phenyleph-
rine. It is believed this is so because they are far more
effective at absorption through the cornea than phenyl-
ephrine itself. Put another way, because they are so
quickly absorbed, lower dose levels can be used to pro-
duce the same ocular effects. Thus, since the dosage
level is lower, the potential risk of side effects is also
significantly lower.

The following examples are set forth as illustrative of
the present invention but should not be construed as
limiting the scope of the invention, since other function-
ally equivalent means will be readily apparent to those
skilled in the art, to use the prodrug invention to
achieve similar results.

EXAMPLE 1

Synthesis of Prodrug of Phenylephrine

(R)-(-)-phenylephrine base (0.83 g, 5 mmole), pi-
valdehyde (0.55 ml, 5 mmole) and benzene (100 ml)
were refluxed together with stirring for 60 hours under
a Dean and Stark trap. The solvent was removed under
reduced pressure to yield the oxazolidine prodrug (92% yield).
The product was recrystallized from benzene and dried.

Physical Measurements

IR (KBr)—2970, 2870, 1600, 1450, 1400, 1375, 1320,
1265, 1220, 1160, 1120, 1070, 970, 860, 780, 700 cm⁻¹,
NMR (CDCl₃) δ = 7.2-6.6 (m, 4H), 5.1-4.8 (m, 1H),
(bs, 1H, 3.5-2.8 (m, 2H), 2.5 (bs, 3H), 1.0 (bs, 9H ppm).
Anal. Calc. for C₁₄H₂₆NO₂: C, 71.46; H, 8.89; N, 5.95.
Found: C, 71.71; H, 8.87; N, 5.93.

Dist. Coeff. (DC) log DC = 1.383 ± 0.013

The reaction as illustrated here is straightforward
involving equimolar amounts of reactants phenyleph-
rine and pivaldehyde, refluxed in a suitable solvent.
Neither time nor temperature appears critical. In this
instance, refluxing and long time were employed to
assure complete reaction. Other suitable solvents inert
to the reactants could be used.

EXAMPLE 2

Preparation of Phenylephrine Formulations

10% Viscous Solution

<table>
<thead>
<tr>
<th>Each Contains</th>
<th>Ingredients</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine Hydrochloride, 10.0%</td>
<td>U.S.P.</td>
<td>20.0 gm</td>
</tr>
</tbody>
</table>

20.0 gm
Solution Preparation

About 120 ml of water is heated to about 80° C. to which is added the methylcellulose powder. The solution is stirred until all the powder is wetted. The heated solution is then placed in an ice bath and cooled until the methylcellulose is fully hydrated or about 45 minutes. To slightly less than 80 ml of water, each ingredient is added until dissolved. Methylcellulose solution is added to the solution containing the other ingredients while stirring. The solution is brought to 200 ml using distilled water.

Oil Suspension Preparation

Because of the instability of the prodrug aqueous solution, an oil suspension was prepared. The parabens and chloroborotanol are dissolved in about 150 gms of sesame oil. The oil may be heated to about 50°C to facilitate the dissolution of each ingredient. The pluronic-P103 is incorporated into the drug powder using a mortar and pestle. The remaining sesame oil is added to the wetted drug powder and triturated until an acceptable slurry is formed. The sesame oil containing the preservatives is added to the slurry to form the suspension. (Butylated hydroxytoluene (0.03%), butylated hydroxyanisole (0.02%) or alpha tocopherol could be added to stabilize the vegetable oil if long term storage is necessary).

EXAMPLE 3

Mydriatic Experiments

The right eye of a normal adult New Zealand Rabbit (3-4 months) was used to measure mydriasis. A flood of diffuse light was placed at a fixed distance from the rabbit eye so that the initial pupil diameter prior to administering eye drops was about 3 mm. Changes in pupil diameter were measured from photographs taken with a 35 mm single lens reflex camera equipped with a close-up lens. Pupil diameters were measured at time 0 through about 5 hours. A dosing volume of 10 μl was administered to the right eye of a group of eight rabbits. A period of at least three days was allowed between instillations of each formulation.

FIGS. 1 and 2 give the results. When the 10% oil suspension of phenylephrine HCl was compared to a molar equivalent concentration of phenylephrine oxazolidine (FIG. 1), the oxazolidine prodrug produced a significantly greater mydriasis in the rabbit eye. The results in FIG. 2 indicate to what extent the prodrug is more potent in comparison to a 10% viscous preparation of phenylephrine HCl. Based upon pupillary diameter the prodrug is approximately 10 times more potent than the aqueous solution of phenylephrine HCl.

EXAMPLE 4

A series of experiments were conducted at 35°C to determine the apparent first order hydrolysis rate constant for phenylephrine oxazolidine at pH 1-7.5. The progress of hydrolysis of the prodrug was followed by measuring the production of pivaldehyde subsequently trapped with thiosemicarbazide (pH<4) or semicarbazide (pH 4-7.5). The resulting formation of the carbazole derivative was followed using UV spectroscopy at 235 and 265 nm (the spectroscopy was a Cary50A UV/VIS Hewlett-Packard, Chicago, Ill.). The prodrug was dissolved in either pH 1, 2, 3, 4, 5, 6, 7 or 7.5 buffered aqueous solutions. The buffers used were hydrochloric acid, formate, acetate and phosphate solutions. The carbonyl trapping reagent was included in the buffer solutions at a concentration of 3.1×10⁻³M. The initial concentration of oxazolidine prodrug was about 1.8×10⁻⁴M. A volume of 3 ml was used for the reaction which was monitored directly in the absorbance cell. The hydrolysis displayed pseudo-first-order kinetics such that the hydrolysis rate constant could be determined from the slope of a linear ln plot of the amount of the amount of carbazole remaining to be formed over time. The concentration of carbazole was calculated by referring to a standard curve.

Results

A half-life of 5-12 minutes was determined for pH's between 1-7.5. It can be seen from the examples presented that the prodrug invention accomplishes all of the enumerated objectives.

What is claimed is:

1. A compound of the formula:

   HO
   O
   C(CH₃)₃
   N
   CH₃

   and the non-toxic pharmaceutically acceptable salt forms thereof.

2. A compound of the formula of claim 1 wherein the compound is 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine.

3. A mydriatic composition for topical, ocular application comprising:
   a small but mydriatically effective amount of the compound 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine suspended in a non-toxic, non-eye-irritating oil suspension.

4. The composition of claim 3 wherein said compound is from about 0.25% by weight to about 10% by weight of the composition.
5. The composition of claim 4 wherein said compound is from about 0.5% by weight to about 5% by weight of said composition.

6. The composition of claim 3 wherein said oil is a mineral oil.

7. The composition of claim 3 wherein said oil is a vegetable oil.

8. The composition of claim 3 wherein said vegetable oil is an edible oil selected from the group consisting of sesame seed oil, cottonseed oil, soybean oil, coconut oil, rapeseed oil, peanut oil, olive oil, palm oil, palm kernel oil, corn oil, sunflower seed oil, castor oil, wallflower oil, and pilchard oil.

9. The composition of claim 8 wherein said oil is sesame seed oil.

10. The composition of claim 3 which includes non-toxic auxiliary substances to enhance the pharmaceutical acceptability of the composition.

11. The composition of claim 3 wherein non-toxic auxiliary substances include anti-bacterials, anti-fungals, anti-oxidants, wetting agents, preservatives, and the like.

12. A method of topically treating the eye to produce a mydriatic effect comprising: applying directly to the cornea a small but mydriatically effective amount of the compound of the formula 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine, said compound being suspended in a non-toxic, non-eye irritating oil suspension.