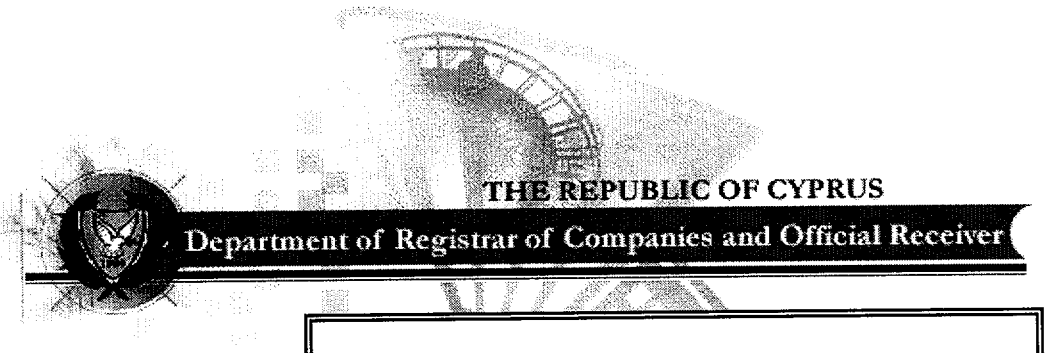

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

THE PATENT OFFICE OF CYPRUS

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ **CY1552**
PUBLICATION NUMBER

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
UK PATENT OFFICE
PUBLICATION NUMBER GB2141339

Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

The document provided hereafter was filed at "The Patent Office" in England under the law CAP.266 before the 1st of April 1998. It was published afterwards by the UK patent office only in English.

(12) UK Patent Application (19) GB (11) 2 141 339 A

(43) Application published 19 Dec 1984

(21) Application No 8413217

(22) Date of filing 23 May 1984

(30) Priority data

(31) 497368 (32) 23 May 1983 (33) US

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(51) INT CL[3]
A61K 31/18

(52) Domestic classification
A5B 180 334 33Y H
U1S 2415 A5B

(56) Documents cited
GB 0993584 US 3341584
J. Pharm. Exper. Therap. 149 2, 1965, pages 183-192.
J. Pharm. Exper. Therap. 164(2), 1968, pages 317-325.
The Extra Pharmacopoeia, Martindale, 28th Edition see pages 1350 etc.
Chemical Abstracts Volume 72, 1970, Number 109665H. (Proc. Soc. Exp Biol. Med. 1970, 133(1), pages 114-119, J. Levy)

(58) Field of search
A5B
C2C

(54) Antiarrhythmic drug

(57) Arrhythmia is prevented or ameliorated by administering *d*-sotalol to lengthen cardiac cell action potential duration without blockade of *beta*-adrenergic receptor sites.

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SPECIFICATION

Antiarrhythmic class III process

This invention relates to a process for treating arrhythmias, and more particularly, to a process for preventing or ameliorating arrhythmia by lengthening cardiac cell action potential duration and refractory period without *beta*-adrenergic blockade by administering an effective dose of dextrorotatory 4-(2-isopropylamino-1-hydroxyethyl)methanesulfonanilide or a pharmaceutically acceptable acid addition salt thereof.

The racemic form of 4-(2-isopropylamino-1-hydroxyethyl)-methanesulfonanilide, disclosed and claimed in Larsen, *et al.*, U.S. Patent No. 3,341,584, is a recognized *beta*-blocking agent known in the biological literature as sotalol or MJ 1999. Pharmacologically, *beta*-blocking compounds reduce sympathetic excitation of the heart and in this respect are considered antiarrhythmics.

Antiarrhythmic drugs are commonly divided into four classes according to their electrophysiological mode of action. Refer to N. Edvardsson, *Current Therapeutic Research, 28*, No. 1 Supplement, pages 113S-118S, July, 1980, and Keefe, *et al., Drugs, 22*, 363-400 (1981) for background information of classification first proposed by E. M. Vaughn Williams: classification of antiarrhythmic drugs, in "Symposium of Cardiac Arrhythmias", pages 449-472, Sandoe, *et al.* (Eds.) A. B. Astra, Soederlalje, Sweden (1970).

Classification of antiarrhythmic Drugs

I. Local Anesthetic Effect
II. Beta-receptor Blockade
III. Prolongation of Action-potential Duration
IV. Calcium Antagonism

Class I agents usually have little or no effect on action potential duration and exert local anesthetic activity directly at cardiac cell membrane. Class II agents show little or no effect on the action potential and exert their effects through competitive inhibition of *beta*-adrenergic receptor sites thereby reducing sympathetic excitation of the heart. Class III agents are characterized by their ability to lengthen the action potential duration thereby preventing or ameliorating arrhythmias. Class IV agents are those which have an antiarrhythmic effect due to their actions as calcium antagonists.

According to the above classification, sotalol is a class III antiarrhythmic agent. N. Edvardsson, *et al, European Heart Journal, 1*, 335-343 (1980); N. Evardsson, *supra.*;D. E. Ward, *et al, Clin. Cardio.2*, 185-191 (1979); D. P. Myburgh, *et al, SA Medical Journal*, 295-298 (August, 1979); L. D. Davis, *et al, Research in Physiology*, 99-114, A. Gaggi Publisher, Bologna (1971); B. N. Singh, *et al., Br.J. Pharma., 39*, 675-687 (1970).Sotalol is also a Class II antiarrhythmic agent in that it reduces sympathetic excitation of the heart by *beta*-blockade.

The active ingredient of the instant process "dextrorotatory 4-(2-isopropylamino-1-hydroxyethyl)methanesulfonanilide" and the corresponding levorotatory stereoisomer have been the subject of biological study and representative publications are listed below. As used in the literature and herein, the racemate form of 4-(2-isopropylamino-1-hydroxyethyl)methanesulfonanilide is at times referred to as sotalol or *dl*-sotalol, the dextrorotatory isomer as *d*-sotalol or (+)-sotalol, and the levorotatory isomer as *l*-sotalol or (−)-sotalol.

D. C. Kvam, *et al., J.Pharm.Exper.Therap., 149*(2), 183-192 (1965) reported that *l-sotalol was about 20-30 times more potent than d*-sotalol in preventing certain metabolic effects such as epinephrine-induced hyperglycemia or hyperlipidemia.

J. V. Levy. *et al., Proc.Soc.Exp.Biol.Med.122*, 373-379 (1966) studied the inotropic and chronotropic effects of sotalol, *d*-sotalol, and *l*-sotalol on rabbit heart atrial preparations and determined that, compared to the racemate, *d*-sotalol was substantially weaker as a *beta*-blocking agent whereas *l*-sotalol was considerably more potent.

P. Somani, *et al., J. Pharm. Exper. Therap., 164*(2), 317-325 (1968)investigated the antiarrhythmic activity of dextro- and levo- rotatory isomers of sotalol in the dog and found that *l*-sotalol, considered the active isomer in terms of blockage of *beta*-receptors, is also the active isomer for specific antiarrhythmic activity (i.e. blockade of adrenergically-induced arrhythmia--Class II). Cardiac arrhythmias induced by oubain or coronary artery ligation were not suppressed by either isomer demonstrating a lack of non-specific antiarrhythmic activity (Class I) seen with other *beta*-adrenergic blocking agents such as the levorotatory and dextrorotatory isomers of pronetholol, propranolol and H56/28. The authors concluded that the antiarrhythmic effects of sotalol are a reflection of the specific *beta*-receptor blocking action of the drug.

Thus, with respect to antiarrhythmic use, there is little in the prior art which would suggest that *d*-sotalol effectively lengthens cardiac cell action potential duration given the relative inactivity of *d*-sotalol as a *beta*-blocking agent.

The present invention is based upon the discovery that *d*-sotalol lengthens the action potential duration of cardiac cells and is thereby useful in treating heart arhythmias. In accordance with the invention, a process is provided for preventing or ameliorating arrhythmia in a mammal comprising administering an effective dose of *d*-sotalol or a pharmaceutically acceptable acid addition salt thereof essentially free of *l*-sotalol to a

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mammal in need thereof to lengthen the action potential duration of ventricular muscle cell without significant *beta*-adrenergic blockade. More particularly, there is provided an antiarrhythmic process comprising administering an effective dose of *d*-sotalol essentially free of *l*-sotalol or a pharmaceutically acceptable acid addition salt thereof to a mammal having arrhythmia or susceptible to arrhythmia to lengthen the action potential duration of cardiac cell sufficiently to produce an antiarrhythmic effect without blocking *beta*-adrenergic receptor sites.

Administration of *d*-sotalol can be carried out orally or parenterally (e.g., intravenous injection) employing liquid or solid form pharmaceutical preparations containing *d*-sotalol as free base or in the form of a pharmaceutically acceptable acid addition salt in combination with a pharmaceutically acceptable carrier.

The dosage administered depends upon the age, state of health, the weight of the recipient, the extent of the disease, the nature of further treatments possible carried out simultaneously and frequency of the treatment. Usually, the effective dose of *d*-sotalol ranges from 0.3-8.6 mg/kg body weight of said mammal. In the case of a human, a dose of from 20 to 600 mg per patient is given from 1 to 4 times per day with oral administration preferred. When *d*-sotalol is administered by the preferred oral route, a larger quantity of *d*-sotalol is required, preferably 160-480 mg once or twice/day, to produce the same effect as a smaller quantity given parenterally, for example by intravenous injection.

The instant process is carried out in accordance with good clinical practice, that is, *d*-sotalol is administered at an effective dose that will produce an increase in action potential duration without causing any harmful or untoward side effects.

Conventional techniques for studying arrhythmias including ambulatory electrocardiography with computer-assisted analysis and programmed stimulation techniques for arrhythmia induction during intracardiac electrophysiological study are employed to determine effectiveness of a specific dose of *d*-sotalol in treating arrhythmias by prolongation of action potential duration. N. Edvardsson, *et al.*, *supra*.Pharmaceutically acceptable acid addition salts of *d*-sotalol are prepared in conventional manner known in the art, for example, by solution of *d*-sotalol in a suitable solvent and addition of the desired acid, for example, in a stoichiometric ratio, and isolation of the salt by standard techniques such as concentration and crystallization. Examples of pharmaceutically acceptable acid addition salts of *d*-sotalol which may be prepared in this manner include salts of inorganic acids such as sulfuric, nitric, phospheroic, and preferably hydrochloric acid, as well as organic acids such as acetic, propionic, succinic, furmaric, maleic, citric, tartaric, cinnamic, lactic, mandelic, ethanedisulfonic acid and the like.

The pharmaceutical compositons of *d*-sotalol employed in the process of the instant invention can be prepared in the conventional way using the common carriers, bindary auxiliaries, and solvents. As previously stated, oral administration is preferred and dosage forms compatible therewith are employed. Compositions suitable for oral administration include conventionally prepared solutions, tablets, capsules, drages, etc. prepared from standard pharmaceutical excipients and carriers such as mannitol, milk sugar, organic or inorganic calcium salts, etc., binders such as polyvinylpyrrolidone, gelatin, or cellulose derivatives, as were tablet dissolving agents such as starch or alginic acid, lubricants such as stearic acid, and inorganic flow agents such as talc or colloidal salicylic acid.

EXAMPLE 1

Resolution of 4-(2-Isopropylamino-1-hydroxyethyl)methanesulfonanilide

d-Sotalol·l-mandelate.-A solution of racemic sotalol (24.5 g., 0.09 mole) (obtained by neutralizing sotalol hydrochloride in ethanol with a mole equivalent of concentrated sodium hydroxide, concentration and extraction of the free base in acetonitrile) in 200 ml. of hot isopropanol was mixed with 13.7 g. (0.09 mole) of *l*-mandelic acid. On cooling, an optically enriched fraction, 26.0 g., m.p. 125-140°, $[\alpha]_D^{25}$ -27.2°, of the *d*-sotalol·*l*-mandelate salt was obtained. Crystallization from isopropanol (300 ml.) afforded 18.7 g., m.p. 139-145.5°, $[\alpha]_D^{25}$ -25.4°.Further recrystallization of this material from 1:1 isopropanol-absolute ethanol provided *d*-sotalol·1-mandelate as white fluffy needles, m.p. 154.5-156°, $[\alpha]_D^{25}$ -14.2°.

*Anal.*Calcd. for $C_{12}H_{20}N_2O_3S \cdot C_8H_8O_3$: C, 56.58; H, 6.65;N, 6.60. Found: C, 56.71; H, 6.82; N, 6.51.

d-Sotalol Hydrochloride.-Acidification of a suspension of *d*-sotalol·*l*-mandelate (10.6 g., 0.025 mole $[\alpha]_D^{25}$ -14.2°) in 150 ml. of isopropanol with 8 ml. of 3.9N ethanolic hydrogen chloride afforded complete solution at reflux temperature. On cooling 7.0 g. (90%) of a white crystalline solid deposited which after crystallization from 20 ml. of methanol and 150 ml. of isopropanol provided 6.0 g. (78%) of analytical product, m.p. 204-205.5°(dec.), $[\alpha]_D^{25}$ +36.0°.

Anal. Calcd. for $C_{12}H_{20}N_2O_3S \cdot HCl$: C, 46.67;H, 6.85; Cl, 11.48. Found: c, 46.81; H, 6.98; Cl, 11.44.

EXAMPLE 2

Electrophysiological Effects of Sotalol, d-Stotaloland 1-Sotalol

Perfused cardiac Purkinje fibers and guinea pig cardiac papillary muscle were stimulated electrically and transmembrane potentials recorded with glass microelectrodes in conventional manner known to the art. L. D. Davis, *et al.*, *Research In Physiology*, Ed. F. F. Kao, *Et al.*, page 99, A. Gaggi, Bologna, 1971.

Evaluation of the test agent was carried out by increasing the concentration in successive steps from 3×10^{-2} ^{7}M up to 3×10^{3}M with each concentration applied during a 30 min. period. The preparations were

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stimulated at 60/min. and transmembrane potentials measured using standard micro-electrode technique.

At concentration between 3×10^{-7}M and 10^{-4}M, sotalol, *d*-sotalol and *l*-sotalol significantly prolonged the action potential duration with nearly identical effects.

EXAMPLE 3

d-Sotalol Class III Action in the Dog

The effects of *d*-sotalol at 10^{-6} to 5×10^{-4}M on the action potentials of ventricular muscle and Purkinge fibers from infarcted (Inf.) and non-infarcted (Non-Inf.) areas was determined in 10 dogs four days after coronary ligation with the following effects at 5×10^{-4}M concentration shown as mean ± standard deviation.

	Ventricular		Purkinge	
	Non-Inf.	Inf.	Non-Inf.	Inf.
Action Potential Duration:				
Control	219 ± 41	173 ± 49	278 ± 42	338 ± 42
d-sotalol	250 ± 44*	201 ± 53*	372 ± 39*	419 ± 68*
Effective Refractory Period:				
Control	215 ± 24	230 ± 37	220 ± 37	248 ± 44
d-Sotalol	244 ± 53*	294 ± 36*	302 ± 44*	367 ± 52*

* p below 0.05 d-sotalol vs. control.

The data demonstrates that in both non-infarcted and infarcted areas, *d*-sotalol significantly prolonged the action potential duration and that the effective refractory period was significantly more prolonged in the infarcted compared to the non-infarcted areas leading to the conclusion that *d*-sotalol has significant Class III effects.

CLAIMS

1. The use of *d*-sotalol essentially free of *l*-sotalol, or of a pharmaceutically acceptable acid addition salt thereof, in the treatment of a mammal having or susceptible to arrhythmia, in order to lengthen the action potential duration of cardiac cell sufficiently to produce an antiarrhythmic effect,substantially without blocking *beta*-adrenergic receptor sites.

2. The use, according to Claim 1, of *d*-sotalol essentially free of *l*-sotalol, or of a pharmaceutically acceptable acid addition salt thereof, wherein the *d*-sotalol or acid addition salt is administered orally to said mammal.

3. The use, according to Claim 1 or Claim 2, of from 0.5 to 8.6 mg of *d*-sotalol essentially free of *l*-sotalol, or of a pharmaceutically acceptable acid addition salt thereof, per kg body weight of said mammal.

4. A composition in unit dosage form suitable for treatment of a mammal having or susceptible to arrhythmia, said composition comprising an antiarrhythmic effective but nontoxic dose of *d*-sotalol essentially free of *l*-sotalol or a pharmaceutically acceptable acid addition salt thereof plus a pharmaceutically acceptable carrier.

5. A composition according to Claim 4 wherein said composition is in a form suitable for parenteral or oral administration to said mammal.

6. A composition according to Claim 5 wherein the antiarrhythmic effective ingredient is *d*-sotalol·*l*-mandelate.

7. A composition according to Claim 5 wherein the antiarrhythmic effective ingredient is *d*-sotalol hydrochloride.

8. A composition according to Claim 4, 5, 6, or 7 wherein said antiarrhythmic effective but nontoxic dose comprises an amount of *d*-sotalol essentially free of l-sotalol within the range of 0.3 to 8.6 mg/kg body weight of said mammal.

9. A medicinal use of *d*-sotalol comprising administering an antiarrhythmic effective but nontoxic dose of *d*-sotalol essentially free of /sotalol or a pharmaceutically acceptable acid addition salt thereof to a mammal having or susceptible to arrhythmia in order to lengthen the action potential duration of cardiac cell sufficiently to produce an antiarrhythmic effect substantially without blocking *beta*-adrenergic receptor sites.

10. A compound characterized in that it is used for lengthening the action potential duration of ventricular muscle cells without significant *bata*-adrenergic blockade, said compound being *d*-sotalol.

11. A compound according to Claim 10 wherein said compound is used for lengthening the action potential duration of cardiac cells.

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12. An antiarrhythmic agent comprising *d*-sotalol essentially free of *l*-sotalol or a pharmaceutically acceptable acid addition salt of said *d*-sotalol essentially free of *l*-sotalol.

13. *d*-Sotalol essentially free of *l*-sotalol, a pharmaceutically acceptable acid addition salt thereof, or a composition according to any of Claims 4 to 8, for use in the treatment of a mammal having or susceptible to arrhythmia.

14. *d*-Sotalol essentially free of *l*-sotalol, a pharmaceutically acceptable acid addition salt thereof, or a composition according to any of claims 4 to 8, when packaged with instructions for use in the treatment of a mammal having or susceptible to arrhythmia.

15. A composition according to Claim 4, substantially as hereinbefore described.

Printed in the UK for HMSO, D8818935, 10/84, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

BNSDOCID: <GB___2141339A__I_>