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(54) **NOVEL METHOD OF TREATMENT**

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(57) **ABSTRACT**

A method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus, which method comprises the administration to a human or non-human mammal in need thereof, of an effective non-toxic amount of an insulin sensitiser so as to provide a plasma concentration of the insulin sensitiser of at least a threshold level (the "Threshold Plasma Concentration") from within the range of effective plasma levels of the insulin sensitiser, compositions for use in such method and methodology for determining plasma concentrations of active agent use in such methods.

Figure 1: Simulated steady-state concentrations of Compound (I) (upper) and M10 (lower) over a 24 hour dosing interval following 4 mg and 8 mg total daily doses of Avandia

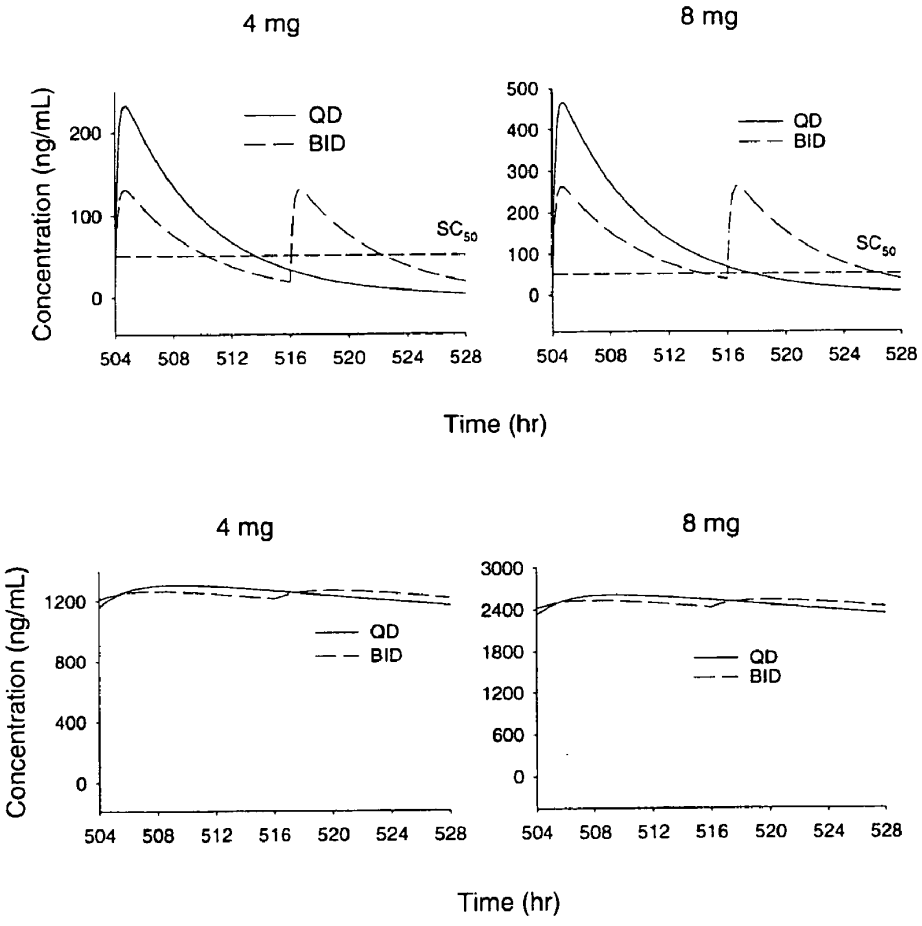
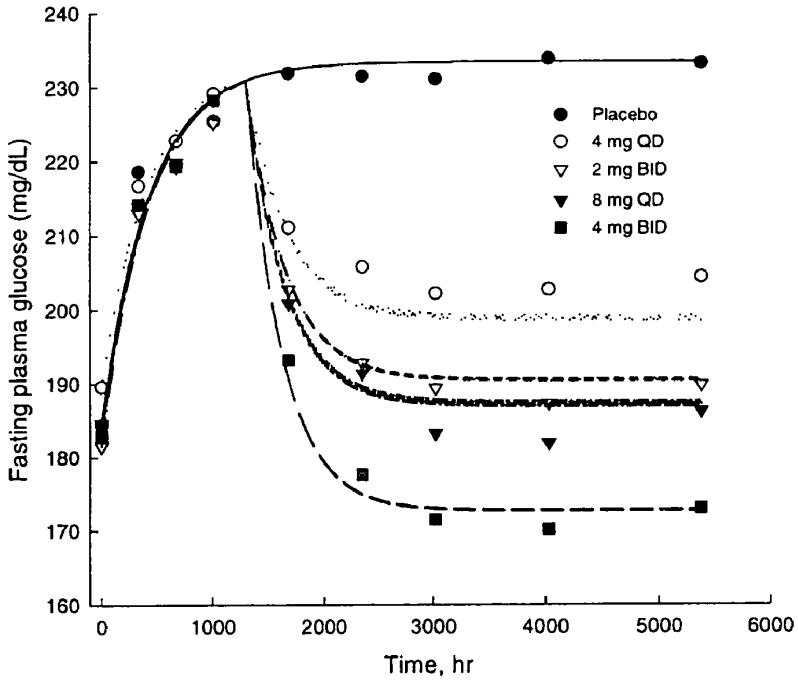


Figure 2: Observed mean fasting glucose concentrations and predicted mean fasting plasma glucose concentrations vs time based on PK/PD modeling of the effect of Compound (I) concentrations by regimen following administration of Avandia



Symbols represent observed FPG, lines represent predicted FPG.

Time scale related to study definition: **0 hr = -6 week**

1008 hr = 0 week (initiation of first dose)

1680 hr = 4 week

NOVEL METHOD OF TREATMENT

FIELD OF THE INVENTION

[0001] This invention relates to a novel method of treatment, in particular to a method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus and a pharmaceutical composition for use in such a method.

BACKGROUND OF THE INVENTION

[0002] European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy] benzyl]thiazolidine-2,4-dione (hereinafter "Compound (I)"). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

[0003] Compound (I) is an example of a class of anti-hyperglycaemic agents known as "insulin sensitisers". In particular Compound (I) is a thiazolidinedione insulin sensitiser.

[0004] European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and U.S. Pat. Nos. 5,104,888 and 5,478,852, also disclose certain thiazolidinedione insulin sensitisers.

[0005] Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as "cyclic insulin sensitisers". Other examples of acyclic insulin sensitisers are those disclosed in U.S. Pat. No. 5,232,945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

[0006] Examples of other insulin sensitisers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and U.S. Pat. No. 5,264,451.

[0007] The above mentioned publications are incorporated herein by reference.

[0008] It is now surprisingly indicated that the particular plasma concentrations of an anti-diabetic agent, such as Compound (I), which provide effective glycaemic control, indeed an optimum effect on glycaemic control, can be determined. This therefore enables optimization of the dosing regimen for the anti-diabetic agent for a given dosing interval. Pharmaceutical compositions which provide plasma concentrations of an anti-diabetic agent, such as Compound (I), at these particular concentrations, especially over an extended period of time, are also envisaged by this invention.

SUMMARY OF THE INVENTION

[0009] Accordingly, in a first aspect, the present invention provides a method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus, which method comprises the administration to a human or non-human mammal in need thereof, of an effective non-toxic amount of an insulin sensitiser, such as Compound (I), so as to provide a plasma concentration of the insulin sensitiser of at least a threshold level from within the range of effective plasma levels of the insulin sensitiser (hereinafter referred to as the "Threshold Plasma Concentration").

DETAILED DESCRIPTION OF THE INVENTOIN

[0010] The Threshold Plasma Concentration is suitably within the range of from 40 to 200 ng/nL including 50 to 200 ng/nL, including 50 to 120 ng/mL, 60 to 120 ng/mL, 90 to 110 ng/mL or 95 to 105 ng/mL.

[0011] A suitable minimum Threshold Plasma Concentration (hereinafter "Minimum Threshold Plasma Concentration") is the SC50 concentration of the particular insulin sensitiser, which for Compound (I) is within the range of 40 to 65 ng/mL, more suitably 41.1 to 61.7, for example 50 or, more suitably, 51.4 ng/mL.

[0012] A preferred Threshold Plasma Concentration (hereinafter "Preferred Threshold Plasma Concentration") is twice the SC50 concentration, which for Compound (I) is in the range of 80 to 130 ng/mL, more suitably 82.2 to 123.4, for example 100 ng/mL or 102.8 ng/mL.

[0013] The invention particularly envisages treatments wherein the plasma concentration of the insulin sensitiser remains substantially within the range of concentrations from the Minimum Threshold Plasma Concentration to the Preferred Threshold Plasma Concentration, that is for Compound (I) within the range of from 40 to 130 ng/mL, more suitably 41.1 ng/mL to 123.4 ng/mL, for example 50 ng/mL to 100 ng/mL or 51.4 ng/mL to 102.8 ng/mL.

[0014] The invention also particularly envisages treatments wherein the plasma concentration of the insulin sensitiser remains substantially within the range of concentrations from the Minimum Threshold Plasma Concentration to a level at or above the Preferred Threshold Plasma Concentration, that is for Compound (I) within the range of from 40 ng/mL to a level at or above 130 ng/mL, more suitably 41.1 ng/mL to a level at or above 123.4 ng/mL, for example 50 ng/mL to 100 ng/mL or 51.4 ng/mL to a level at or above 102.8 ng/mL.

[0015] In its preferred form, the invention provides a treatment wherein the plasma concentration of the insulin sensitiser remains substantially at or above the Preferred Threshold Plasma Concentration, that is for Compound (I), substantially at or above 100 ng/mL, especially substantially at or above 102.8 ng/mL.

[0016] A suitable thiazolidinedione insulin sensitiser is Compound (I).

[0017] Other suitable thiazolidinedione insulin sensitisers include 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl-)methoxy]benzyl]thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone).

[0018] A particular thiazolidinedione insulin sensitiser is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione (or pioglitazone).

[0019] A particular thiazolidinedione insulin sensitiser is 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone).

[0020] When the insulin sensitiser is Compound (I), the unit dose suitably comprises 2 to 12 or preferably 4 to 8 mg of Compound (I) in a pharmaceutically acceptable form.

[0021] Suitable unit dosages of other insulin sensitisers are those indicated in publications mentioned herein and include from 100 to 800 mg of troglitazone such as 200, 400, 600 or 800 mg and for pioglitazone from 5 to 50 mg, including 10 to 40 mg, such as 20, 30 or 40 mg and also including 15, 30 and 45 mg of pioglitazone.

[0022] As indicated above, the treatment of the invention is suitably effected by the administration of a pharmaceutical composition of the insulin sensitiser adapted so as to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser.

[0023] Accordingly, in a further aspect, the invention also provides a pharmaceutical composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier therefor, which composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser, suitably over a sustained period of time.

[0024] Suitable modified release compositions are delayed, pulsed or sustained release compositions.

[0025] Accordingly, in a further aspect, the invention also provides a modified release pharmaceutical composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier therefor, which composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser, suitably over a sustained period of time.

[0026] Suitably the carrier is adapted to provide the provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration.

[0027] Suitably the modified release is a sustained release, for example providing effective release of active agents of at least a Threshold Plasma Concentration over a time period of up to 24 hours.

[0028] Suitably the modified release is a pulsed release, for example providing two pulses of release of active agents of at least a Threshold Plasma Concentration per 24 hours.

[0029] The invention particularly envisages compositions adapted to provide a plasma concentration of the insulin sensitiser which remains substantially within the range of concentrations from the Minimum Threshold Plasma Concentration to the Preferred Threshold Plasma Concentration, that is for Compound (I) within the range of from 40 to 130 ng/mL, more suitably 41.1 to 123.4 ng/mL, for example 50 to 100 ng/mL or 51.4 to 102.8 ng/mL.

[0030] The invention also envisages compositions adapted to provide a plasma concentration of the insulin sensitiser which remains substantially at or above the Preferred Threshold Plasma Concentration, that is for Compound (I), substantially at or above 100 ng/mL, especially substantially at or above 102.8 ng/mL.

[0031] Suitably the composition is a unit dose composition.

[0032] Suitably, the Threshold Plasma concentration of the insulin sensitiser is maintained or exceeded over several hours, for example 12, 16 or 24 hours, per dose of insulin sensitiser.

[0033] Suitably, the treatment is such that the Threshold Plasma concentration of the insulin sensitiser is maintained or exceeded over a sustained period of time.

[0034] It will be understood that the insulin sensitiser, such as Compound (I), is administered in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate of the relevant pharmaceutically active agent. It will be understood that all pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

[0035] Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in EP 0306228 and WO94/05659. A preferred pharmaceutically acceptable salt is a maleate.

[0036] Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

[0037] Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

[0038] Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures thereof. Compound (I) contains a chiral carbon atom, and hence can exist in up to two stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

[0039] The insulin sensitisers mentioned herein are prepared in accordance with known methods, for example those disclosed in the above mentioned publications or in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press).

[0040] When used herein the term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

[0041] When used herein the term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

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