USE OF LANDIOLOL HYDROCHLORIDE IN THE LONG-TERM TREATMENT OF TACHYARRHYTHMIAS

The invention provides a new use of landiolol hydrochloride for persistent reduction of the heart rate and/or blood pressure during the administration period compared to the heart rate and/or blood pressure before administration in the treatment of a human suffering from tachycardia or tachyarrhythmia and/or hypertension, wherein landiolol hydrochloride is administered at a constant dose of at least 5 µg/kg/min, specifically of at least 10 µg/kg/min for a period of at least 2 hours and wherein the heart rate and/or blood pressure of said patient is persistently reduced during the administration period compared to the heart rate and/or blood pressure before treatment.

BACKGROUND

Tachyarrhythmia generally refers to a heart rate that is faster than 90 beats per minute. In case of severe coronary stenosis or other severe cardiac diseases heart rates faster than 80 bpm may be considered too high (relative tachycardia).

Tachyarrhythmias may be responsible for worsening heart failure, stroke, myocardial infarction or sudden death. They may be primary or occur secondary to underlying cardiac, pulmonary or endocrine disease.

Tachyarrhythmias can be either physiologic such as sinus tachycardia occurring during exercise or pathologic as during atrial or ventricular tachycardia which can occur when irritable cells in the heart muscle or heart's electrical conduction system start to fire faster than the heart's normal rhythm. Tachyarrhythmias can start in either the upper heart chambers (atria) or lower heart chambers (ventricles). An atrial (= supraventricular) tachyarrhythmia starts in the atria and is generally classified as being atrial tachycardia (AT), atrial flutter, or tachycardic atrial fibrillation (AF). A ventricular tachyarrhythmia starts in the ventricles and is generally classified as being either a ventricular tachycardia (VT) or ventricular fibrillation (VF).

Supraventricular tachyarrhythmia is a major post-operative complication, and develops with the high frequency of 11-40% after coronary artery bypass surgery; therefore, this condition plays an important role in increased postoperative complications and duration of hospitalization (Murakami M., et al., Drug Metab. Pharmacokinet., 2005, 20(5), 337-344).

Tachycardia can be life-threatening because it can lead to ventricular fibrillation, in which the heart beats rapidly in a chaotic, purposeless fashion such that the heart cannot pump blood effectively to the body. If untreated, fibrillation can be fatal.

Long-standing tachycardia is well recognized for its potential to induce a dilated cardiomyopathy. While the exact incidence of tachycardia-mediated cardiomyopathy remains unclear, an association between tachycardia and cardiomyopathy has been recognized. Virtually every form of supraventricular tachyarrhythmia, including ectopic atrial tachycardia, nonparoxysmal junctional tachycardia, and atrial fibrillation (AF), has been associated with reversible left ventricular dysfunction or "cardiomyopathy." The development of a cardiomyopathy has also been documented with ventricular tachyarrhythmias and frequent ventricular premature beats.

Tachyarrhythmias are often treated with ß-blockers which have been reported to be effective regulators of heart rate and sinus rhythm. Beta-blockers were considered useful specifically for the short and long term treatment of such diseases. These ß adrenergic receptor-antagonists competitively block beta receptors, thereby inhibiting cAMP formation and preventing the events that routinely follow. $ß_1$ receptor blockade causes a decrease in cardiac inotropy, chronotropy, and automaticity, culminating in a reduction of cardiac output.

There are three subgroups of beta receptors. Although these receptors may be found in more than one location in the human body, $ß_1$ receptors are primarily found on cardiac myocytes, $ß_2$ receptors are located chiefly in vascular and bronchial smooth muscle, $ß_3$ receptors are concentrated in adipocytes, although being found in cardiac myocytes, too. During stressful conditions, endogenous catecholamine release stimulates $ß_1$ receptors to promote an increase in the heart rate and contractility, whereas $ß_2$ receptor stimulation induces branchiolar and arteriolar dilation. Agonists also promote insulin release glycogenolysis, and gluconeogenesis (Anderson A.C., 2008, Clin.Ped.Emergency Med., 4-16).

Blockade of $ß_1$ receptors also leads to suppression of renin secretion in the kidney, thereby decreasing production of angiotensin II (a potent vasoconstrictor) and aldosterone (which promotes sodium retention). The combination of renal effects and reduced cardiac output promotes a decrease in the blood pressure. Blocking vascular smooth muscle $ß_2$ receptors provides a rise in vascular tone that is clinically insignificant in most instances.

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarised by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). This equals the maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100–140 mmHg systolic (top reading) and 60–90 mmHg diastolic (bottom reading). High blood pressure is said to be present if it is often at or above 140/90 mmHg.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Hypertension puts strain on the heart, leading to hypertensive heart disease and coronary artery disease if not treated. Hypertension is also a major risk factor for stroke, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease and is a cause of chronic kidney disease. A moderately high arterial blood pressure is associated with a shortened life expectancy while mild elevation is not. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although drug treatment is still often necessary in people for whom lifestyle changes are not enough or not effective.

Esmolol hydrochloride, the first ultra short-acting adrenergic ß1 adrenoreceptor blocking agent, has been widely used to aid control of tachycardia and hypertension. Esmolol is an ultra short-acting intravenous cardioselective beta-antagonist. It has an extremely short elimination half-life (mean: 9 minutes; range: 4 to 16 minutes) and a total body clearance [285 ml/min/kg (17.1 L/h/kg)] approaching 3 times cardiac output and 14 times hepatic blood flow. The alpha-distribution half-life is approximately 2 minutes. When esmolol is administered as a bolus followed by a continuous infusion, onset of activity occurs within 2 minutes, with 90% of steady-state beta-blockade occurring within 5 minutes. Full recovery from beta-blockade is observed 18 to 30 minutes after terminating the infusion. Esmolol blood concentrations are undetectable 20 to 30 minutes post infusion. The elimination of esmolol is independent of renal or hepatic function as it is metabolised by red blood cell cytosol esterases to an acid metabolite and methanol. The acid metabolite, which is renally eliminated, has 1500-fold less activity than

esmolol. Clinically, esmolol was used in the past for the following: (i) situations where a brief duration of adrenergic blockade is required, such as tracheal intubation and stressful surgical stimuli; and (ii) critically ill or unstable patients in whom the dosage of esmolol is easily titrated to response and adverse effects are rapidly managed by termination of the infusion. In adults, bolus doses of 100 to 200 mg are effective in attenuating the adrenergic responses associated with tracheal intubation and surgical stimuli. For the control of supraventricular arrhythmias, acute postoperative hypertension and acute ischaemic heart disease, doses of < 300 μg/kg/min, administered by continuous intravenous infusion, are used. The principal adverse effect of esmolol is hypotension (incidence of 0 to 50). The incidence of hypotension appears to increase with doses exceeding 150 μg/kg/min and in patients with low baseline blood pressure. Hypotension infrequently requires any intervention other than decreasing the dose or discontinuing the infusion. Symptoms are generally resolved within 30 minutes after discontinuing the drug. In surgical and critical care settings where clinical conditions are rapidly changing, the pharmacokinetic profile of esmolol allows the drug to provide rapid pharmacological control and minimises the potential for serious adverse effects.

Miwa Y. et al. (2010, Circulation Journal, 74, 856-863) describe the effect of landiolol in the treatment of electrical refractory storm.

Takahashi S. et al. (2000, Can.J.Anesth., 47, 265-272) describe studies on the effect of landiolol on hemodynamic response to acute theophylline intoxication inducing tachyarrhythmia in animals.

Morisaki A. et al. (2012, Gen.Thorac.Cardiovasc.Surg., 60, 386-390) describes continuous very-low-dose of 2 μg/kg/min – 5 μg/kg/min of landiolol for about 10 days in treating postoperative atrial tachycardia in patients with poor left ventricular function.

Wariishi S. et al. (2009, Interactive Cardiovasc. Thoracic Surgery, 9, 811-813) describes the low dose administration of landiolol hydrochloride in patients with postoperative supraventricular arrhythmia.

Studies on different doses of landiolol hydrochloride infused for eleven minutes during anesthesia in patients of different age and sex are disclosed by Mizuno J. et al. (2007, Eur.J.Clin.Pharmacol., 63, 243-252).

Kubo K. et al. (2005, J.Anesth., 19, 174-176) describe the use of landiolol at a dose of 40ug/kg/min during cesarean section in a patient with Romano-Ward syndrome. Administration was stopped 10 minutes before end of surgery.

Nagai R. et al. (2013, Circulation J., 77, 908-916) disclose the use of landiolol to control tachycardia in patients with left ventricular dysfunction. The dosage is adjusted to the range of 1-10 µg/kg/min.

It was shown that long-term administration of beta-blockers can be associated with an increase in myocardial ß-adrenergic receptor density (Hellbrunn S. et al., Circulation, 1989, 79, 483-490, Nanoff C. et al., 1990, Basic Res. Cardiol., 85, 88-95). The ß-adrenergic receptor increase may not only lead to the restoration of ß-adrenergic sensitivity in cases of heart failure treatment but, in cases of tachycardia, it may also lead to a beta-blocker tolerance which thus needs increased dosages and shorter administration intervals.

It has been reported that sudden discontinuation of the administration of similar compounds (propranolol hydrochloride) from patients who suffered from angina or other coronary heart diseases worsened the condition or led to cardiac infarction (Harrison DC and Alderman EL, 1976, Chest, 69(1), 1-2; Hausen T., 1981, MMW Münch Med Wochenschr., 123(42), 1583-4). In data sheets for Ono Act (landiolol hydrochloride, Ono Pharmaceuticals. Revised edition Nov. 2012) and esmolol hydrochloride (Brevibloc, Aug. 10, 2009) it is noted that careful observation is required when discontinuing the administration of landiolol or that an overshoot after termination of esmolol administration cannot be ruled out.

Additionally, sensitization of receptor mediated response may lead to withdrawal syndromes after termination of beta-blocker administration (Peters J.R. et al., 1985, 107, 43-52).

Furthermore, long term treatment with intravenously administered beta-blockers can lead to negative side effects such as infusion site reactions including inflammation and induration, like edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation phlebitis, which side effects are commonly minimized by administering the diluted formulation.

There is still an unmet demand for providing a long-term treatment of tachyarrhythmia or tachycardia that avoids negative side effects but are effective in the treatment without the need

of increasing the dosage due to tolerance effects thereby promoting vascular irritation and overshoot reactions.

BRIEF DESCRIPTION

The object of the disclosure is solved by the present disclosure.

The present disclosure also provides in one aspect the use of a formulation of landiolol hydrochloride in the manufacture of a medicament for persistent reduction of the heart rate in a subject suffering from supraventricular tachycardia and/or hypertension, wherein said landiolol hydrochloride is a lyophilized powder reconstituted to obtain a ready to use solution or a formulation wherein landiolol is provided in a diluted ready to use solution which is to be administered at a constant dose of more than 5 μg/kg/min for a period of at least 2 hours.

The disclosure provides a formulation of landiolol hydrochloride in a therapeutically efficient amount for use in the treatment of a subject suffering from tachycardia, tachyarrhythmia and/or hypertension, wherein landiolol hydrochloride is administered at a constant dose of about 5 μg/kg/min, specifically more than (>) 5 μg/kg/min, preferably at least 10 μg/kg/min for a period of at least 2 hours, preferably for at least 4 hours, preferably for at least 6 hours, preferably for at least 12 hours, preferably for at least 20 hours, preferably for at least 24 hours, preferably for at least 2 days, preferably for more than two days and wherein the heart rate and/or blood pressure of said patient are persistently reduced during the administration period compared to the heart rate and/or blood pressure before treatment, specifically as opposed to other short acting beta blocker such as esmolol.

According to a further embodiment of the disclosure, the constant dose of landiolol hydrochloride is at least 15 μg/kg/min, specifically at least 20 μg/kg/min, specifically at least 25 μg/kg/min, specifically at least 30 μg/kg/min, specifically at least 35 μg/kg/min, specifically at least 40 μg/kg/min.

According to a further embodiment of the disclosure the heart rate and/or blood pressure are reduced at least 5%, preferably between 10% and 50% compared to the heart rate and/or blood pressure before treatment with landiolol.

Overshoot is not occurring after termination of administration and normal heart rate and/or blood pressure are attained within a few minutes, specifically within 5 to 20 minutes and more specifically, said normal heart rate and/or blood pressure are preserved for at least 30 minutes, preferably for at least 60 minutes, more preferred at least 120 minutes after termination of administration of landiolol-hydrochloride as opposed to esmolol where an overshoot occurs within minutes and may be maintained hours thus leading to increased heart rate and/or blood pressure.

According to the disclosure, the formulation thus shows a reduced or no overshoot effect with regard to the heart rate and/or blood pressure after termination of administration.

According to an embodiment of the disclosure, landiolol-hydrochloride is at a concentration of about 1 to 30 mg/mL, preferably about 5 to 15 mg/mL.

According to the embodiment of the disclosure, the administration of a pharmaceutical composition comprising landiolol-hydrochloride for the use according of the present invention, may be done in a variety of ways, including orally, subcutaneously, intravenously, intraarterially, intracoronary, intranasally, intraotically, transdermally, mucosally, topically, e.g., gels, salves, lotions, creams, etc., intraperitoneally, intramuscularly, intrapulmonary, e.g. employing inhalable technology or pulmonary delivery systems, vaginally, parenterally, rectally, or intraocularly.

A specific embodiment provides a formulation wherein landiolol hydrochloride is a lyophilized powder reconstituted to obtain a ready to use i.v. solution, optionally the i.v. solution has a pH of up to 6.5 and as a further option, said i.v. solution is administered as continuous infusion.

According to an embodiment, said i.v. solution is administered as maintenance infusion at a dose of between 5 to 100 µg/kg/min, preferably 10 to 100 µg/kg/min, preferably between 10 to 50 µg/kg/min.

In an embodiment, the i.v. solution is local tissue tolerant at the infusion site, preventing local venous irritation or skin necrosis at the infusion site.

In a specific embodiment, the subject is suffering from supraventricular tachycardia.

In a further specific embodiment, the subject is suffering from hypertension, specifically from primary or secondary hypertension or hypertensive crisis.

The inventive use is specifically for treating a subject, wherein said subject is

a. suffering from tachycardia selected from, supraventricular tachycardia, ventricular tachycardia, hypertension and non-compensatory sinus tachycardia, atrial tachycardic fibrillation, atrial flutter in perioperative, postoperative, or other circumstances where persistent control of the ventricular rate is desirable, or

b. in need of blood pressure lowering perioperatively or in other acute situations or during aortic dissection or for controlled hypotension to avoid blood loss in ear, nose, or throat surgery or for diagnostic purposes.

Specifically, said subject is having cardiac decompensation and/or hyperhydratation and/or renal decompensation and/or hypernatremia and/or hyperchloramic acidosis and/or hyperhydratation.

According to a further embodiment, the formulation or preparation is used for a subject receiving a positive inotropic drug, specifically selected from the group of Berberine, Calcium, Calcium sensitisers like Levosimendan, cardiac myosin activators like Omecamt iv, Catecholamines selected from the group of Dopamine, Dobutamine, Dopexamine, Epinephrine (adrenaline), Isoprenaline (isoproterenol), Norepinephrine (noradrenaline), ephedrine, Digoxin, Digitalis; eicosanoids like Prostaglandins; phosphodiesterase inhibitors selected from the group of Enoximone, Milrinone, Amrinone, Theophylline; Glucagon or Insulin or a sympathomimetic drug, specifically selected from the group of ß agonists.

According to a specific embodiment, the subject that can be treated using the formulation of the invention is suffering from intoxication from positive inotropic drug or sympathomimetic drug.

Additionally, also a method of producing a ready-to-use solution of landiolol hydrochloride for the inventive use is provided by reconstituting a lyophilized powder consisting of pure landiolol hydrochloride with a solvent, wherein said solvent is optionally devoid of alcohol, in an amount necessary to obtain a ready-to-use solution at a concentration of about 5 to 15 mg/mL.

As a further embodiment, a formulation is provided where landiolol is present in an already diluted ready to use preparation.

DETAILED DESCRIPTION OF THE INVENTION

It could surprisingly be shown that landiolol-hydrochloride, being an ultra short-effective beta-blocker, can be used for long term administration without showing any tolerance effects thus leading to a persistent reduction of heart rate and avoiding any overshoot effect upon termination of the administration.

This effect could not be shown by another ultra short-effective beta blocker, esmolol. Long term administration of esmolol leads to a relative increase of the heart rate and blood pressure

already after 60 minutes of administration demonstrating the absence of any overt beta blocking effect and additionally, after termination of administration, the heart rate and blood pressure raise immediately over control values.

Long term administration of landiolol-hydrochloride can also achieve heart rate values and/or blood pressure values which are significantly lower than the heart rate and/or blood pressure values achieved under esmolol long-term treatment. Thus, the invention provides a new use of landiolol hydrochloride as a parenteral formulation in the treatment of a subject suffering from tachycardia, tachyarrhythmia and/or hypertension, wherein landiolol-hydrochloride is administered for a period of at least 2 hrs, specifically for a period of at least 2.5 hrs, specifically for a period of at least 3 hrs, specifically at least 4 hrs, specifically for a period of at least 5 hrs, specifically at least 6 hrs, specifically at least 8 hrs, specifically at least 10 hrs, specifically at least 12 hrs, specifically at least 14 hrs, specifically at least 16 hrs, specifically at least 18 hrs, specifically at least 20 hrs, specifically at least 24 hrs, specifically at least 2 days, specifically for more than two days and wherein the heart rate of said patient is persistently reduced during the administration period compared to the heart rate before landiolol hydrochloride treatment.

Landiolol (CAS 133242-30-5), administered as landiolol hydrochloride (CAS 144481-98-1), chemical name (−)-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 3-[4-[(S)-2-hydroxy-3-(2-morpholinocarbonylamino) ethylamino] propoxy] phenylpropionate monohydrochloride, empirical formula $C_{25}H_{39}N_3O_8HCl$ (molecular weight 546.05) is an ultra-short acting β1-selective blocker.

The term “heart rate” means the heart beats per minute.

The term “blood pressure” means systolic and diastolic blood pressure expressed in mmHg or kPa.

The term “constant” with regard to the administration of landiolol-hydrochloride means that the dose is not changed during the respective time period, thus there is no steady increase or decrease of dosage during said time interval.

Thus the patient can be administered a high dose landiolol-hydrochloride for long term treatment without the side effects of tolerance or overshoot reaction. The term “normal” heart rate is related to a heart rate while the subject is relaxed but awake, in a neutrally temperate

environment, and not having recently exerted himself or herself nor having been subject to stress. The typical normal (resting) heart rate in adults is 60–80 beats per minute (bpm), heart rates between 50 and 60 are also considered normal under resting conditions or during sedation.

The terms "tachycardia" and "tachyarrhythmia" as used herein are understood in the broadest sense, including all disease conditions associated with fast or irregular heart rate, in particular a condition in which the heart contracts at a rate greater than 90-100/min in adults. In some cases, specifically in case of severe coronary stenosis or other severe cardiac diseases, heart rates above 80 bpm may be considered too high (relative tachycardia).

Herein tachycardia specifically refers to pathologic tachycardia accompanying anoxia, such as that caused by anaemia; congestive heart failure; haemorrhage; or shock. Tachycardia acts to increase the amount of oxygen delivered to the cells of the body by increasing the rate at which blood circulates through the vessels.

Herein, the term "supraventricular tachycardia" (SVT) defines a condition presenting as a rapid heart rhythm originating at or above the atrioventricular node. Although SVT can be due to any supraventricular cause, the term is most often used to refer to a specific example, paroxysmal supraventricular tachycardia (PSVT), two common types being atrioventricular reciprocating tachycardia and AV nodal reentrant tachycardia.

In general, SVT is caused by one of two mechanisms: The first is re-entry; the second is automaticity. Re-entry (such as AV nodal reentrant tachycardia and atrioventricular reciprocating tachycardia) often presents with an almost immediate onset with sudden increase in heart rate. A person experiencing this type of PSVT may feel the heart rate accelerate from 60 to 200 beats per minute or more. Typically, when it reverts to normal rhythm, this is also sudden.

The main pumping chamber, the ventricle, is protected (to a certain extent) against excessively high rates arising from the supraventricular areas by a 'gating mechanism' at the atrioventricular node, which allows only a proportion of the fast impulses to pass through to the ventricles. In a condition called Wolff-Parkinson-White Syndrome, a 'bypass tract' avoids this node and its protection and the fast rate may be directly transmitted to the ventricles. This situation has characteristic findings on ECG.

In automatic types of SVT (atrial tachycardia, junctional ectopic tachycardia), there is more typically a gradual increase and decrease in the heart rate. These are due to an area in the heart that generates its own electrical signal.

Supraventricular tachycardias can be contrasted with the potentially more dangerous ventricular tachycardias rapid rhythms that originate within the ventricular tissue.

The term “hypertension” or, as equivalent “high blood pressure” or “arterial hypertension”, is a medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarised by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). This equals the maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100–140 mmHg systolic (top reading) and 60–90 mmHg diastolic (bottom reading). High blood pressure is said to be present if it is at or above 140/90 mmHg. Severely elevated blood pressure, i.e. equal to or greater than a systolic 180 or diastolic of 110, sometimes termed malignant or accelerated hypertension, is referred to as a "hypertensive crisis", as blood pressure at this level confers a high risk of complications.

Herein the terms “subject” refers to human beings in need of such treatment.

According to a further embodiment, it surprisingly turned out that the typical side effects of local venous skin irritations or inflammatory reactions at the site of injection induced by esmolol could be avoided by long-term administration of landiolol-hydrochloride using the formulation according to the invention, specifically long term treatment did not bring about any blushing, erythema, pain, inflammation, induration, phlebitis and thrombosis.

“Long-term administration” means an administration which takes at least 30 minutes.

“High dose” means a dose of landiolol of more than 20 µg/kg/min, specifically more than 25 µg/kg/min, more than 30 µg/kg/min, more than 35 µg/kg/min, more preferably more than 40 µg/kg/min.

Persistent reduction means that the heart rate and/or blood pressure are constantly lower than the heart rate and/or blood pressure immediately before start of the landiolol hydrochloride administration. Persistent reduction of the heart rate and/or blood pressure may be due to the lack of developing a tolerance syndrome by the subject. Thereby, the sensitivity of the subject

towards the administration of the beta blocker is not significantly increased which further has the advantage that termination of the administration of the beta blocker does not result in hypersensitivity towards ß adrenergic agonists being administered or are circulating in the subject´s blood stream.

According a specific embodiment of the invention, landiolol hydrochloride can be combined with any ß adrenergic agonist treatment, for example it can be combined with positive inotropic substances like dobutamine or amrinone or with any other known $ß_1$ and $ß_2$ stimulating agents.

According to a specific embodiment, the heart rate and/or blood pressure are reduced at least 1%, preferably at least 2%, preferably at least 3%, preferably at least 4%, preferably at least 5%, preferably between 10% and 50% compared to the heart rate before treatment.

"Rebound effect" is the emergence or re-emergence of symptoms that were either absent or controlled while taking a medication, but appear when the same medication is discontinued or reduced in dosage In the case of re-emergence, the severity of the symptoms is often worse than pretreatment levels.

An overshoot effect can occur after termination of the medication with a severe raise of heart rate as opposed to the achievement of a normal heart rate. Severe raise means that the heart rate and blood pressure is 2.5%, specifically 5%, specifically 10%, specifically more than 10%, more specifically more than 25% higher compared to the heart rate before treatment. Alternatively, the increase of the heart rate can be indicated by an increase of 10 to 30 bpm and/or an increase of the blood pressure by 5-30 mmHg. An overshoot effect can specifically occur when the administration of the active compound is immediately terminated without stepwise reduction of the administration dosage.

"Tolerance" occurs when providing long term treatment, specifically when administrating beta blocker one usually must consider the possibility of occurrence of habituation towards the drug which makes it necessary to increase the dosage and/or interval of administering said medicament or to change the active agent used for the treatment of the specific symptom or disease. Tolerance necessitates an increase in dosage to achieve the same drug effect.

Thus, according to an embodiment of the invention, tolerance and overshoot effects are avoided or significantly reduced after long term administration of landiolol-hydrochloride and normal heart rate and/or blood pressure are achieved within a few minutes, specifically within 5 to 20

minutes after termination of the administration of landiolol-hydrochloride and said effect being continuing for at least 15 minutes, specifically at least 30 minutes, specifically at least 60 minutes, more specifically at least 120 minutes after the administration of landiolol-hydrochloride.

Specifically, no significant overshoot effect occurs after termination of administration of landiolol-hydrochloride.

In contrast, esmolol shows a significant tolerance and overshoot effect thus leading to significantly increased heart rate and blood pressure that are above normal pre dose values.

According to the invention any composition comprising landiolol hydrochloride as active agent may be used which is available at present and applicable for application.

Said landiolol HCl compositions may contain different concentrations of landiolol, for example, but not limited to 10 mg, 12.5 mg, 20 mg, 50 mg, 300 mg or 600 mg.

The formulation of the invention can be present in any form which can be used for administration, in particular as pharmaceutical preparation.

Administration of a pharmaceutical composition comprising landiolol-hydrochloride for the use according to the present invention may be done in a variety of ways. It may be administered parenterally, orally, optically, vaginally, mucosally, nasally, rectally, topically , e.g., gels, salves, lotions, creams, etc., or buccally.

The term “parenteral” as used herein refers to subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intrarterial, intrasynovial, intrasternal, intrathecal, intralesional, intraperitoneal, intratracheal, intracranial, intracoronar, intrapulmonary, e.g. employing inhalable technology or pulmonary delivery systems.

Exemplary formulations as used for parenteral administration include those suitable for subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution, emulsion or suspension.

For example, the formulation of the invention can be administered as liquid or powder. It can be administered topically, intravenously, subcutaneously, by inhalation, e.g. to administer an aerosol, or by using a nebulizer, or in orally available form like tablets or capsules.

Aerosolized delivery of the landiolol hydrochloride may result in a more homogeneous distribution of the agent in a lung, so that deep lung delivery is obtained.

The formulation can be administered with any pharmaceutically acceptable substances or carriers or excipients as known in the art. These can be for example, but are not restricted to water, neutralizing agents like NaOH, KOH, stabilizers, DMSO, saline, betaine, taurine etc.

Any stabilizers, preservatives, buffers, tonicity agents or excipients may further be comprised in the parenteral formulations. Specifically, stabilising agents may be, but are not limited to polyethylene glycol, cyclodextrin, ethanol. Buffer agents may be, but are not limited to, sodium hydroxide, glacial acetic acid, hydrochloric acid, sodium acetate dehydrate, potassium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate anhydride. As an example, the tonicity agent may be sodium chloride and as example of an excipient, mannitol may be used.

The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S.

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the pharmaceutical composition is administered. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable excipients include starch, glucose, lactose, sucrose, gelatine, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. The formulation should be selected according to the mode of administration.

Landiolol-hydrochloride may further be provided as a lyophilized powder which is reconstituted to obtain a ready to use i.v. solution or as aqueous solution. Alternatively, the solutions may be diluted and prepared from stock solutions by adjusting the respective concentration of landiolol-hydrochloride. As a further alternative, landiolol may be already provided in a diluted ready to use preparation.

Said formulations may be, for example, available under the trade names Rapibloc ®, Onoact ® or Corebeta ®.

According to one embodiment, the landiolol hydrochloride formulation comprises landiolol HCl and D-mannitol.

The pH of the formulation may be between 6 and 7, specifically about 6.5.

According to an embodiment of the invention, landiolol-hydrochloride is at a concentration of about 1 to 30 mg/mL, specifically about 10 to 20 mg/mL, specifically about 5 to 15 mg/mL.

The formulation may be administered parenterally, more specifically intravenously. For long term treatment, continuous infusion is the preferred administration form, the solution may specifically administered as maintenance infusion at a dose of between 0.1 to 100 µg/kg/min, specifically between 5 to 50 µg/kg/min, more specifically between 10 to 50 µg/kg/min.

Whereby the formulation due to its excellent local tolerability can be administered using peripheral veins.

The administration of landiolol hydrochloride after at least two hours at constant dose can be terminated immediately or the dose can also be stepwise reduced, either within a short period of several minutes or hours As an alternative, the dose of landiolol hydrochloride can also be increased after the minimum period of two hours, i.e. it may be increased up to 40 µg/kg/min or even more than 40 µg/kg/min, depending on the need of the patient and the condition. Said increase of dosage can be gradually or stepwise.

The present invention specifically provides the use of landiolol-hydrochloride for long term treatment of subjects suffering from tachycardia selected from supraventricular tachycardia, ventricular tachycardia or hypertension and non-compensatory sinus tachycardia, atrial fibrillation, atrial flutter in perioperative, postoperative, or other circumstances where persistent control of the ventricular rate is desirable, or subjects who are in need of blood pressure lowering, for example perioperatively or in other acute situations or during aortic dissection, or for controlled hypotension to avoid blood loss in ear, nose, or throat surgery or for diagnostic purposes.

The invention also provides a method of treating subjects suffering from tachycardia selected from supraventricular tachycardia, ventricular tachycardia and non-compensatory sinus tachycardia, atrial fibrillation, atrial flutter in perioperative, postoperative, or other circumstances where persistent control of the ventricular rate is desirable, or subjects in need of

blood pressure lowering, for example perioperatively or in other acute situations or during aortic dissection, or for controlled hypotension to avoid blood loss in ear, nose, or throat surgery or for diagnostic purposes.

Landiolol hydrochloride long term treatment may also be used for subjects having cardiac decompensation, hyperhydratation, renal decompensation, hypernatremia, hyperchloramic acidosis and/or hyperhydratation.

The administration of positive inotropic drugs may lead to severe side effects like the development of tachycardia (see for example Alhashemi J.A. et al., Brit.J.Anaesthes., 2005, 95(5), 648-650).

According to a further embodiment, the formulation is used for a subject receiving a positive inotropic drug or is suffering from intoxication due to the administration of an inotropic drug, specifically selected from the group of Berberine, Calcium, calcium sensitisers like Levosimendan, cardiac myosin activators like Omecamtiv, catecholamines selected from the group of Dopamine, Dobutamine, Dopexamine, Epinephrine (adrenaline), Isoprenaline (isoproterenol), Norepinephrine (noradrenaline), ephedrine, Digoxin, Digitalis; Eicosanoids like Prostaglandins; phosphodiesterase inhibitors selected from the group of Enoximone Milrinone, Amrinone, Theophylline; Glucagon or Insulin or a sympathomimetic drug, specifically selected from the group of $ß_1$ and or $ß_2$ agonists.

The invention provides the use of landiolol hydrochloride for persistent reduction of the heart rate and/or blood pressure during the administration period of landiolol hydrochloride for producing a medicament for the treatment of a human suffering from tachycardia, tachyarrhythmia and/or hypertension, wherein landiolol hydrochloride is administered at a constant dose of at least 5 µg/kg/min, specifically of > 5 µg/kg/min for a period of at least 2 hours.

The invention also provides a method of treating a patient with tachycardia or tachyarrhythmia, specifically with supraventricular tachycardia, and/or hypertension, wherein said patient is administered a constant dose of more than 5 µg/kg/min, specifically at least 10 µg/kg/min landiolol hydrochloride for a period of at least 1.5 hours, specifically of at least 2 hours and wherein the heart rate of said patient is thereby persistently reduced during the administration period compared to the patient´s heart rate before treatment.

According to a specific embodiment of the invention, a treatment regimen is provided wherein the subject is administered a) 5 µg/kg/min landiolol hydrochloride for two hours, b) 10 µg/kg/min are administered for two hours and c) 40 µg/kg/min is administered for at least two hours.

The invention furthermore comprises the following items:

1. Formulation of landiolol hydrochloride for persistent reduction of the heart rate and/or blood pressure during the administration period of landiolol hydrochloride in the treatment of a human suffering from tachycardia, tachyarrhythmia and/or hypertension, wherein landiolol hydrochloride is administered at a constant dose of at least 5 µg/kg/min for a period of at least 1.5 hours, preferably for a period of at least 2 hours.

2. The formulation for use according to item 1, wherein the constant dose of landiolol hydrochloride is more than 5 µg/kg/min, specifically at least 10 µg/kg/min, specifically at least 15 µg/kg/min, specifically at least 20 µg/kg/min, specifically at least 25 µg/kg/min, specifically at least 30 µg/kg/min, specifically at least 35 µg/kg/min, specifically at least 40 µg/kg/min.

3. The formulation for use according to items 1 or 2, wherein landiolol hydrochloride is administered for at least 3 hours, preferably for at least 4 hours, preferably for at least 6 hours, preferably for at least 12 hours, preferably for at least 24 hours, preferably for at least 2 days, preferably for more than two days.

4. The formulation for use according to items 1 to 3, wherein the heart rate is reduced at least 5%, preferably between 10% and 50% compared to the heart rate before treatment.

5. The formulation for use according to items 1 to 4, wherein no overshoot effect occurs after termination of administration of landiolol hydrochloride.

6. The formulation for use according to items 1 to 5, wherein a normal heart rate is reached within 5 to 20 minutes after termination of administration.

7. The formulation for use according to items 1 to 6, wherein said landiolol hydrochloride is at a concentration of about 1 to 30 mg/mL, preferably about 5 to 15 mg/mL.

8. The formulation for use according to items 1 to 7, wherein said landiolol hydrochloride is a lyophilized powder reconstituted to obtain a ready to use solution or a formulation wherein landiolol is provided in a diluted ready to use preparation.

9. The formulation for use according to items 1 to 8, wherein said solution has a pH of up to 6.5.

10. The formulation for use according to items 1 to 9, wherein said solution is administered as oral, subcutaneous, intravenous, intraarterial, intracoronary, intranasal, transdermal, topical, interpulmonary administration, specifically said solution is administered as continuous intravenous infusion, optionally using peripheral veins.

11. The formulation for use according to items 1 to 10, wherein said solution is administered as maintenance infusion at a dose of between 15 to 100 µg/kg/min, preferably between 10 to 50 µg/kg/min.

12. The formulation for use according to items 1 to 11, wherein said solution is local tissue tolerant at the infusion site, preventing local venous irritation or skin necrosis at the infusion site.

13. The formulation for use according to items 1 to 12 in the treatment of supraventricular tachycardia.

14. The formulation for use according to items 1 to 12 in the treatment of hypertension.

15. The formulation for use according to any one of items 1 to 14, wherein said subject is

a) suffering from tachycardia selected from, supraventricular tachycardia, ventricular tachycardia, non-compensatory sinus tachycardia, atrial fibrillation, atrial flutter and/or hypertension in perioperative, postoperative, or other circumstances where persistent control of the ventricular rate is desirable, or

b) in need of blood pressure lowering or for diagnostic purposes.

16. The formulation for use according to items 1 to 15, wherein said subject is having cardiac decompensation, hyperhydratation, renal decompensation, hypernatremia, hyperchloramic acidosis and/or hyperhydratation.

17. The formulation according to items 1 to 16, wherein said subject receiving a positive inotropic drug, specifically selected from the group of dobutamine, amrinone or a sympathomimetic drug, specifically selected from the group of beta 1, beta 2 agonists. phophodiesterease inhibitors or Calcium sensitizers.

18. Formulation according to items 1 to 17, wherein said subject is suffering from intoxication from positive intotropic and/ or chronotropic drug or sympathomimetic drug.

The examples described herein are illustrative of the present invention and are not intended to be limitations thereon. Different embodiments of the present invention have been described according to the present invention. Many modifications and variations may be made to the techniques described and illustrated herein without departing from the spirit and scope of the invention. Accordingly, it should be understood that the examples are illustrative only and are not limiting upon the scope of the invention.

EXAMPLES:

Example 1:

A single centre prospective, randomized, double blind, crossover, pharmacokinetic, safety and tolerability study to compare long-term infusion administration of AOP LDLL600 against esmolol in healthy volunteers was performed.

Landiolol hydrochloride lyophilized (LDLL600) comprises 600 mg landiolol hydrochloride, 600 mg mannitol, pH 6.5. The primary packing of LDLL600 is 50 ml vial, the reconstitution volume is 50 ml and the final product concentration is 12 mg/mL landiolol HCl.

Study:

12 subjects were administered AOP LDLL600 or Esmolol (Brevibloc, 2500 mg/250 ml) in 1:1 ratio in double-blind, randomized, cross-over setting. PK, systemic cardiovascular and local tolerability and safety of the 24 h-long term infusions of three dose levels of both IMPs during each treatment period were assessed.

	Landiolol	Esmolol	Duration
Low, µg/kg/min	10	50	2 h
Medium, µg/kg/min	20	100	2 h
High, µg/kg/min	40	200	20 h

Landiolol was infused over 24 h in a dose of 10 µg/KG/min (2hrs), followed by 20 µg/KG/min (2hrs), followed by 40 µg/KG/min for 20 hrs.

Dosing algorithm was body weight divided by 20, 10 and 5 in ml/h giving 10, 20 and 40 µg/KG/min at a concentration of 12 mg/ml. No severe adverse drug reactions, mild local reactions, 1 severe local reaction (Esmolol High Dose).

Local tolerability of Landiolol compared to Esmolol is clearly better:

Local reactions Landiolol: 2/12 (16,7%)

Esmolol: 7/14 (50,0%)

Table 1:

		Landiolol	Esmolol	p<
Control		67,8	67	
	Time (min)			
low	12	62,7	65,2	0,258
	16	60,3	65,4	0,016
	30	59,5	62,6	0,205
	60	57,8	63,6	0,035
	120	56,2	63,8	0,004
medium	240	56,1	63,7	0,033
high	720	57,5	67,9	0,001
	1200	53,6	67,9	0,001
end	1440			
	Time after administration (min):			
	12	63,5	74,7	0,003
	16	67	74	0,033
	30	70	76,8	0,033
	60	69,2	73,1	0,096
	120	66,8	70,2	0,233

Example 2:

A single centre prospective, randomized, double blind, crossover, pharmacokinetic, safety and tolerability study to compare long-term infusion administration of AOP LDLL600 against esmolol in healthy volunteers was performed.

Landiolol hydrochloride lyophilized (LDLL600) comprises 600 mg landiolol hydrochloride, 600 mg mannitol, pH 6.5. The primary packing of LDLL600 is 50 ml vial, the reconstitution volume is 50 ml and the final product concentration is 12 mg/mL landiolol HCl.

Study:

12 subjects were administered AOP LDLL600 or Esmolol (Brevibloc, 2500 mg/250ml) in 1:1 ratio in double-blind, randomized, cross-over setting. PK, systemic cardiovascular and local tolerability and safety of the 24 h-long term infusions of three dose levels of both IMPs during each treatment period were assessed.

	Landiolol	Esmolol	Duration
Low, µg/kg/min	10	50	2 h
Medium, µg/kg/min	20	100	2 h
High, µg/kg/min	40	200	20 h

Landiolol was infused over 24 h in a dose of 10, 20 and 40 µg/KG/min, i.e. 10µg/KG/min landiolol were administered for 2hrs, followed by 2hrs administration of 20 µg/KG/min and further followed by 20 hrs administration of 40 µg/KG/min.
Post-infusion follow up measurements were performed immediately after 20 hrs administration study, i.e. 2, 4 min etc. after stop of landiolol administration.
Dosing algorithm was body weight divided by 20, 10 and 5 in ml/h giving 10, 20 and 40 µg/KG/min at a concentration of 12 mg/ml. No severe adverse drug reactions, mild local reactions, 1 severe local reaction (Esmolol High Dose).
Tolerance state (esmolol, MD, HD): the results of table 2 show that even the dosage x 100% (> high dose) does not provide any additive effect.

L=LDLL600
E = Esmolol
LD = low dose, MD = medium dose, HD = high dose; FU = post-infusion follow up

Table 2

	Time point	Mean (SD)	Mean (SD)	p-value*	
Landiolol	Predose	67.3 (8.18)			
L^{LD}	2 min	65.6 (5.09)	-1.8 (7.77)	0.718	
	3 min	64.8 (6.82)	-2.5 (7.48)	0.484	
	4 min	64.6 (6.97)	-2.8 (6.38)	0.196	
	6 min	65.7 (8.78)	-1.7 (7.97)	0.461	
	8 min	63.8 (6.57)	-3.6 (9.07)	0.392	
	12 min	62.7 (7.71)	-4.7 (10.99)	0.213	
	16 min	60.3 (6.72)	-7.1 (5.32)	0.003	
	20 min	60.0 (6.05)	-7.3 (10.51)	0.031	
	30 min	59.5 (8.55)	-7.8 (12.55)	0.071	
	60 min	57.8 (8.05)	-9.6 (11.89)	0.010	
	90 min	58.1 (7.14)	-9.3 (11.33)	0.006	
	2 h	56.2 (5.89)	-11.2 (11.75)	0.004	
L^{MD}	Predose	56.2 (5.89)	-11.2 (11.75)	0.004	
	2 min	56.3 (6.48)	-11.1 (10.73)	<.001	
	3 min	57.6 (5.02)	-9.8 (7.90)	0.003	
	4 min	56.4 (6.87)	-10.9 (9.26)	<.001	
	6 min	56.2 (7.86)	-11.2 (11.10)	0.002	
	8 min	57.7 (7.24)	-9.7 (10.96)	0.001	
	12 min	54.5 (6.07)	-12.8 (10.17)	<.001	
	16 min	56.9 (6.88)	-10.4 (11.42)	0.002	
	20 min	54.5 (6.86)	-12.8 (10.52)	0.001	
	30 min	58.3 (8.53)	-9.0 (11.92)	0.014	
	60 min	56.0 (5.17)	-11.3 (9.86)	0.001	
	90 min	57.2 (6.79)	-10.2 (10.81)	<.001	
	2 h	56.1 (7.38)	-11.3 (9.41)	<.001	
L^{HD}	Predose	56.1 (7.38)	-11.3 (9.41)	<.001	
	2 min	57.8 (5.43)	-9.6 (8.69)	0.002	
	3 min	57.4 (6.40)	-9.9 (9.92)	0.004	
	4 min	54.8 (5.45)	-12.6 (9.52)	<.001	
	6 min	57.7 (7.38)	-9.7 (11.01)	0.010	
	8 min	56.7 (6.62)	-10.7 (10.76)	<.001	
	12 min	57.9 (8.13)	-9.4 (12.21)	0.022	
	16 min	56.0 (6.80)	-11.3 (10.71)	0.002	
	20 min	55.9 (6.35)	-11.4 (9.74)	<.001	
	30 min	56.8 (7.23)	-10.5 (10.30)	<.001	
	60 min	61.9 (8.93)	-5.4 (13.14)	0.226	
	90 min	62.5 (5.95)	-4.8 (11.24)	0.146	

	2 h	64.3 (5.25)	-3.0 (9.59)	0.516	
	4 h	60.4 (5.25)	-6.9 (11.24)	0.049	
	8 h	57.5 (5.96)	-9.8 (10.39)	0.002	
	12 h	56.5 (6.08)	-10.8 (10.17)	<.001	
	16 h	53.6 (4.89)	-13.8 (10.01)	<.001	
	20 h (end)	61.7 (5.87)	-5.7 (11.51)	0.087	
Landiolol Infusion stop					
L^{FU}	Predose	61.7 (5.87)	-5.7 (11.51)	0.087	
	20 h 2 min	60.6 (5.50)	-6.8 (11.98)	0.105	
	20 h 4 min	60.8 (4.04)	-6.5 (9.88)	0.054	
	20 h 6 min	61.4 (5.43)	-5.9 (9.79)	0.083	
	20 h 8 min	61.7 (5.33)	-5.7 (10.63)	0.104	
	20 h 12 min	63.5 (6.11)	-3.8 (10.00)	0.334	
	20 h 16 min	67.0 (8.92)	-0.3 (14.69)	0.556	
	20 h 20 min	67.0 (8.29)	-0.3 (11.89)	0.834	
	20 h 30 min	70.0 (5.70)	2.7 (9.47)	0.301	
	21 h	69.2 (9.64)	1.8 (12.70)	0.609	
	22 h	66.8 (8.43)	-0.5 (9.97)	0.634	
	24 h	71.5 (4.96)	4.2 (10.34)	0.169	
	26 h	72.6 (5.26)	5.3 (9.97)	0.085	

Esmolol					
E^{LD}	Predose	67.6 (7.87)			
	2 min	66.9 (6.28)	-0.7 (6.22)	0.540	
	3 min	65.7 (4.91)	-1.9 (5.34)	0.171	
	4 min	65.6 (6.44)	-2.1 (7.64)	0.278	
	6 min	66.0 (4.52)	-1.6 (5.96)	0.380	
	8 min	65.5 (4.35)	-2.1 (7.05)	0.368	
	12 min	65.2 (4.74)	-2.4 (6.77)	0.198	
	16 min	65.4 (5.51)	-2.3 (7.58)	0.434	
	20 min	65.6 (7.07)	-2.0 (9.49)	0.402	
	30 min	62.6 (5.05)	-5.1 (6.29)	0.011	
	60 min	63.6 (4.67)	-4.1 (8.00)	0.123	
	90 min	64.1 (4.99)	-3.5 (6.55)	0.075	
	2 h	63.8 (4.89)	-3.9 (7.12)	0.050	
E^{MD}	Predose	63.8 (4.89)	-3.9 (7.12)	0.050	
	2 min	63.4 (7.88)	-4.3 (10.36)	0.063	
	3 min	62.6 (5.50)	-5.1 (8.40)	0.047	
	4 min	64.9 (9.04)	-2.7 (8.96)	0.155	
	6 min	63.9 (5.10)	-3.8 (7.45)	0.114	
	8 min	62.1 (4.46)	-5.6 (7.54)	0.007	

	12 min	61.8 (5.07)		0.016	
	16 min	64.1 (5.02)	-3.5 (7.14)	0.093	
	20 min	62.6 (4.33)	-5.0 (7.34)	0.024	
	30 min	62.1 (5.00)	-5.6 (8.20)	0.017	
	60 min	66.2 (5.04)	-1.4 (10.41)	0.722	Tolerance state
	90 min	65.4 (6.17)	-2.2 (8.59)	0.669	Tolerance state
	2 h	63.7 (4.86)	-3.9 (7.75)	0.091	Tolerance state
E^{HD}	Predose	63.7 (4.86)	-3.9 (7.75)	0.091	Tolerance state
	2 min	65.1 (7.10)	-2.5 (8.96)	0.330	Tolerance state
	3 min	64.4 (4.38)	-3.2 (8.99)	0.248	Tolerance state
	4 min	64.5 (4.74)	-3.1 (8.16)	0.221	Tolerance state
	6 min	64.9 (4.29)	-2.8 (8.97)	0.434	Tolerance state
	8 min	63.9 (7.14)	-3.7 (10.45)	0.186	Tolerance state
	12 min	64.8 (4.39)	-2.9 (9.19)	0.400	Tolerance state
	16 min	64.4 (7.16)	-3.3 (8.32)	0.274	Tolerance state
	20 min	67.3 (7.26)	-0.4 (11.69)	0.941	Tolerance state
	30 min	65.4 (5.69)	-2.3 (9.26)	0.467	Tolerance state
	60 min	72.6 (6.64)	4.9 (9.60)	0.064	Tolerance state
	90 min	73.6 (4.57)	5.9 (8.95)	0.025	Tolerance state
	2 h	73.9 (4.55)	6.2 (9.32)	0.040	Tolerance state
	4 h	70.4 (5.03)	2.8 (9.60)	0.246	Tolerance state
	8 h	67.9 (5.95)	0.3 (10.34)	0.577	Tolerance state
	12 h	68.4 (8.30)	0.7 (10.94)	0.436	Tolerance state
	16 h	67.9 (7.49)	0.3 (9.27)	0.724	Tolerance state
	20 h (end)	69.1 (6.40)	1.5 (9.05)	0.421	Tolerance state
Esmolol Infusion stop					
E^{FU}	Predose	69.1 (6.40)	1.5 (9.05)	0.421	
	20 h 2 min	69.0 (4.88)	1.4 (7.57)	0.516	
	20 h 4 min	71.3 (7.04)	3.6 (8.77)	0.151	
	20 h 6 min	**73.1 (7.89)**	**5.4 (8.11)**	**0.025**	**overshoot**
	20 h 8 min	**73.1 (7.57)**	**5.4 (8.10)**	**0.028**	**overshoot**
	20 h 12 min	**74.7 (8.62)**	**7.1 (8.43)**	**0.004**	**overshoot**
	20 h 16 min	**74.0 (7.99)**	**6.4 (7.44)**	**0.009**	**overshoot**
	20 h 20 min	**74.4 (7.04)**	**6.8 (7.17)**	**0.005**	**overshoot**
	20 h 30 min	**76.8 (8.51)**	**9.1 (8.04)**	**<.001**	**overshoot**
	21 h	**73.1 (7.50)**	**5.5 (8.15)**	**0.032**	**overshoot**
	22 h	70.2 (7.06)	2.6 (8.02)	0.208	
	24 h	72.1 (7.37)	4.5 (9.51)	0.090	
	26 h	72.8 (9.74)	5.1 (10.85)	0.097	

*Wilcoxon signed-rank test of difference from zero for changes from the last measurement before the start of the first IMP administration in treatment period

CLAIMS

1. Use of a formulation of landiolol hydrochloride in the manufacture of a medicament for persistent reduction of the heart rate in a subject suffering from supraventricular tachycardia and/or hypertension, wherein said landiolol hydrochloride is a lyophilized powder reconstituted to obtain a ready to use solution or a formulation wherein landiolol is provided in a diluted ready to use solution which is to be administered at a constant dose of more than 5 μg/kg/min for a period of at least 2 hours.

2. The use according to claim 1, wherein the constant dose of landiolol hydrochloride is at least 10 μg/kg/min, at least 15 μg/kg/min, at least 20 μg/kg/min, at least 25 μg/kg/min, at least 30 μg/kg/min, at least 35 μg/kg/min, or at least 40 μg/kg/min.

3. The use according to claims 1 or 2, wherein landiolol hydrochloride is to be administered for at least 4 hours, for at least 6 hours, for at least 12 hours, for at least 24 hours, for at least 2 days, or for more than two days.

4. The use according to any one of claims 1 to 3, wherein the heart rate is reduced at least 5%, or between 10% and 50% compared to the heart rate before treatment.

5. The use according to any one of claims 1 to 4, wherein no overshoot effect occurs after termination of administration of landiolol hydrochloride.

6. The use according to any one of claims 1 to 5, wherein a normal heart rate is reached within 5 to 20 minutes after termination of administration.

7. The use according to any one of claims 1 to 6, wherein said landiolol hydrochloride is at a concentration of about 1 to 30 mg/mL, or about 5 to 15 mg/mL.

8. The use according to any one of claims 1 to 7, wherein said solution has a pH of up to 6.5.

9. The use according to any one of claims 1 to 8, wherein said solution is to be administered intravenously.

10. The use according to any one of claims 1 to 9, wherein said solution is to be administered as maintenance infusion at a dose of between 15 to 100 µg/kg/min, or between 10 to 50 µg/kg/min.

11. The use according to any one of claims 1 to 10, wherein said solution is local tissue tolerant at the infusion site, preventing local venous irritation or skin necrosis at the infusion site.

12. The use according to any one of claims 1 to 11, wherein said subject is suffering from supraventricular tachycardia and/or hypertension in perioperative, postoperative, or other circumstances where persistent control of the ventricular rate is desirable, wherein said supraventricular tachycardia is selected from the group consisting of atrial fibrillation and atrial flutter.

13. The use according to any one of claims 1 to 12, wherein said subject is having cardiac decompensation, renal decompensation, hypernatremia, hyperchloramic acidosis and/or hyperhydratation.

14. The use according to any one of claims 1 to 13, wherein said subject is receiving a positive inotropic drug, selected from the group of dobutamine, amrinone or a sympathomimetic drug, or selected from the group of beta 1, beta 2 agonists, phophodiesterease inhibitors or Calcium sensitizers.

15. The use according to any one of claims 1 to 14, wherein said subject is suffering from intoxication from positive inotropic and/ or chronotropic drug or sympathomimetic drug.