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(56) Documents Cited:
WO 2021/201680 A1 **CN 111150738 A**
CN 104127397 B **CN 103142643 B**
RU 002742505 C1
Trials, vol. 22, no. 1, 2021, Muller Marie et al., "Impact of intravenous lidocaine on clinical outcomes of patients with ARDS during COVID-19 pandemia (LidoCovid): A structured summary of a study protocol for a randomised controlled trial.", p. 131.
Bone Marrow Transplantation, vol. 28, no. 1, Voltarelli J C et al., "Beneficial effect of intravenous lidocaine in cutaneous chronic graft-versus-host disease secondary to donor lymphocyte infusion", p. 97-99.
LUNG, vol. 182, no. 1, 2004, Huang T K et al., "Surfactant Lavage with Lidocaine Improves Pulmonary Function in Piglets after HCl-Induced Acute Lung Injury", p. 15-25.

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COMPOSITION AND METHOD OF TREATMENT

INTRODUCTION

[0001] The present invention relates to a composition and method for treating an autoimmune disease or a condition in which an immune response caused by a disease or infection needs treating. Such an immune response is one causing hyper-inflammation, such as, but not limited to a cytokine storm, giving rise to Acute Respiration Distress Syndrome (ARDS) or Cytokine Storm Syndrome (CSS) as can occur in SARS-CoV-2 disease (COVID-19).

BACKGROUND

[0002] The COVID-19 pandemic has meant many groups have been urgently looking at the repurposing of approved drugs that might address the symptoms of COVID-19.

[0003] Acute respiratory distress syndrome (ARDS) is the main cause of morbidity and mortality in Coronavirus disease 19 (Covid-19) for which, as of now, there is no effective treatment besides respiratory support and the use of high dose dexamethasone.

[0004] Many drugs, for example chloroquine and ivermectin, have been studied on hospitalized patients with severe manifestations of SARS-CoV-2 infection, but none have shown to be successful.

[0005] ARDS is caused, and sustained, by an uncontrolled inflammatory activation characterized by a massive release of cytokines (cytokine storm), diffuse lung edema, inflammatory cell infiltration and disseminated coagulation. Macrophage and T lymphocyte dysfunction plays a central role in this syndrome.

[0006] In several experimental *in vitro* and *in vivo* models, many of these pathophysiological changes are triggered by stimulation of the P2X7 receptor.

[0007] In this regards, viral pathogens in the respiratory tract cause cellular stress and a subsequent innate immune response. This causes massive exocytosis of ATP, resulting in high extracellular ATP concentrations. Initially, this stimulates the purinergic P2Y2 and P2X4 receptors, resulting in a short period of surfactant exocytosis, but as ATP levels continue to rise, the P2X4 and P2Y2 receptors become insensitive, and the normal release of surfactant is prevented. When the extracellular levels of ATP start to exceed the lower threshold for the activation of the P2X7 extracellular ATP receptors (P2X7Rs) located on the cell surface of the innate immune cells, it causes a pro-inflammatory response of the innate immunity, followed by a massive release of inflammatory mediators and a subsequent cytokine storm. The resulting vascular leakage and pulmonary edema induce

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the disaggregation and inactivation of pulmonary surfactant, a key element in the pathogenesis of ARDS that ends in alveolar collapse and reduced gas exchange.

[0008] Applicant hypothesized that this P2X7 receptor might be an ideal candidate to target in Covid-19-associated ARDS. Unfortunately, most of the known P2X7 receptor blockers become toxic when given to a patient at dose levels required for effective treatment.

[0009] They hypothesised that auto immune diseases might also be treated by the same approach – namely, blocking of the P2X7 receptor, using lidocaine at an effective dose.

[0010] A first object of the invention was to identify a drug or drugs for use in treating such diseases.

[0011] A second and further object was to formulate such a drug for such use.

[0012] A third and further object was to deliver such drugs in a manner, and at a dose, which facilitated effective treatment.

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BRIEF SUMMARY OF THE DISCLOSURE

[0013] In accordance with a first aspect of the present invention there is provided lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS), wherein the Lidocaine or a salt thereof is formulated with a lipophilic excipient for subcutaneous, oromucosal or sublingual delivery, to target the lymphatic system, and comprises a unit dose of from 40-100mg of lidocaine or a salt thereof in a volume of less than or equal to 0.5ml.

[0014] In one embodiment it causes a cytokine storm.

[0015] The autoimmune disease may be any of those listed below:

- Achalasia
- Addison's disease
- Adult Still's disease
- Agammaglobulinemia
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-GBM/Anti-TBM nephritis
- Antiphospholipid syndrome
- Autoimmune angioedema
- Autoimmune dysautonomia
- Autoimmune encephalomyelitis
- Autoimmune hepatitis
- Autoimmune inner ear disease (AIED)
- Autoimmune myocarditis
- Autoimmune oophoritis

- Autoimmune orchitis
- Autoimmune pancreatitis
- Autoimmune retinopathy
- Autoimmune urticaria
- Axonal & neuronal neuropathy (AMAN)
- Baló disease
- Behcet's disease
- Benign mucosal pemphigoid
- Bullous pemphigoid
- Castleman disease (CD)
- Celiac disease
- Chagas disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA)
- Cicatricial pemphigoid
- Cogan's syndrome
- Cold agglutinin disease
- Congenital heart block
- Coxsackie myocarditis
- CREST syndrome
- Crohn's disease
- Dermatitis herpetiformis
- Dermatomyositis
- Devic's disease (neuromyelitis optica)
- Discoid lupus
- Dressler's syndrome
- Endometriosis
- Eosinophilic esophagitis (EoE)
- Eosinophilic fasciitis
- Erythema nodosum
- Essential mixed cryoglobulinemia
- Evans syndrome
- Fibromyalgia
- Fibrosing alveolitis
- Giant cell arteritis (temporal arteritis)
- Giant cell myocarditis
- Glomerulonephritis
- Goodpasture's syndrome
- Granulomatosis with Polyangiitis
- Graves' disease
- Guillain-Barre syndrome
- Hashimoto's thyroiditis
- Hemolytic anemia
- Henoch-Schonlein purpura (HSP)
- Herpes gestationis or pemphigoid gestationis (PG)
- Hidradenitis Suppurativa (HS) (Acne Inversa)
- Hypogammalglobulinemia
- IgA Nephropathy
- IgG4-related sclerosing disease
- Immune thrombocytopenic purpura (ITP)
- Inclusion body myositis (IBM)
- Interstitial cystitis (IC)
- Juvenile arthritis
- Juvenile diabetes (Type 1 diabetes)

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- Juvenile myositis (JM)
- Kawasaki disease
- Lambert-Eaton syndrome
- Leukocytoclastic vasculitis
- Lichen planus
- Lichen sclerosus
- Ligneous conjunctivitis
- Linear IgA disease (LAD)
- Lupus
- Lyme disease chronic
- Meniere's disease
- Microscopic polyangiitis (MPA)
- Mixed connective tissue disease (MCTD)
- Mooren's ulcer
- Mucha-Habermann disease
- Multifocal Motor Neuropathy (MMN) or MMNCB
- Multiple sclerosis
- Myasthenia gravis
- Myelin Oligodendrocyte Glycoprotein Antibody Disorder
- Myositis
- Narcolepsy
- Neonatal Lupus
- Neuromyelitis optica
- Neutropenia
- Ocular cicatricial pemphigoid
- Optic neuritis
- Palindromic rheumatism (PR)
- PANDAS
- Paraneoplastic cerebellar degeneration (PCD)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Parry Romberg syndrome
- Pars planitis (peripheral uveitis)
- Parsonage-Turner syndrome
- Pemphigus
- Peripheral neuropathy
- Perivenous encephalomyelitis
- Pernicious anemia (PA)
- POEMS syndrome
- Polyarteritis nodosa
- Polyglandular syndromes type I, II, III
- Polymyalgia rheumatica
- Polymyositis
- Postmyocardial infarction syndrome
- Postpericardiotomy syndrome
- Primary Biliary Cholangitis
- Primary sclerosing cholangitis
- Progesterone dermatitis
- Psoriasis
- Psoriatic arthritis
- Pure red cell aplasia (PRCA)
- Pyoderma gangrenosum
- Raynaud's phenomenon
- Reactive Arthritis
- Reflex sympathetic dystrophy
- Relapsing polychondritis

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- Restless legs syndrome (RLS)
- Retroperitoneal fibrosis
- Rheumatic fever
- Rheumatoid arthritis
- Sarcoidosis
- Schmidt syndrome
- Scleritis
- Scleroderma
- Sjögren's syndrome
- Sperm & testicular autoimmunity
- Stiff person syndrome (SPS)
- Subacute bacterial endocarditis (SBE)
- Susac's syndrome
- Sympathetic ophthalmia (SO)
- Takayasu's arteritis
- Temporal arteritis/Giant cell arteritis
- Thrombocytopenic purpura (TTP)
- Thyroid eye disease (TED)
- Tolosa-Hunt syndrome (THS)
- Transverse myelitis
- Type 1 diabetes
- Ulcerative colitis (UC)
- Undifferentiated connective tissue disease (UCTD)
- Uveitis
- Vasculitis
- Vitiligo
- Vogt-Koyanagi-Harada Disease

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[0016] Of these, those in which Cytokine Storm Syndrome presents, are particular targets for treatment.

[0017] Lidocaine, also known as lignocaine is sold under the brand name Xylocaine®. It is a local anaesthetic of the amino amide type.

[0018] As an approved medicine it is used intravenously, subcutaneously, topically and orally.

[0019] However, intravenously it is not particularly suited to targeting the lymphatic system and treating hyper-inflammation by blocking the P2X7 receptors, thus stopping the "cytokine storm" which can be the cause of life-threatening ARDS in SARS-COV-2 disease (COVID-19) and other autoimmune diseases.

[0020] Thus, the invention provides a pharmaceutical composition comprising lidocaine or a salt thereof which is formulated to facilitate uptake by the lymphatic system by the incorporation of one or more suitable excipients.

[0021] Furthermore, it is preferably packaged in a delivery form, and with instructions, for subcutaneous, oromucosal or sublingual administration.

[0022] Essentially, the Lidocaine is dissolved in one or more lipophilic.

[0023] The use of long chain fatty acids and/ or surface modifiers such as polyethylene glycol (PEG) and/ or surfactants are preferred.

[0024] Favoured delivery systems include, but are not limited to, nanoparticles, microspheres, liposomes, emulsifying drug delivery systems (EDDS) and variants thereof e.g. self-emulsifying drug delivery systems (SEDDS), self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS).

[0025] The simplest forms are drugs in oils such as medium chain triglycerides.

[0026] Thus, suitable formulations may include functional excipients, such as lipophilic and polar solvents, co-solvents, viscosity modifiers, surfactants, sweeteners and flavourants.

[0027] To make it palatable the formulation includes a sweetener, e.g. saccharin and a flavourant, e.g. a banana flavour.

[0028] To facilitate their solubility in a low volume formulation, (less than 1ml and more preferably still less than 0.5ml) a polar solvent is also used. A preferred polar solvent is ethanol.

[0029] Additionally, one or more co-solvents are used. Suitable co-solvents include polyethylene glycol (Macrogol 400) and propylene glycol (E 1520).

[0030] A problem with using Lidocaine is its' known toxicity.

[0031] Local anesthetics, such as lidocaine, can cause methemoglobinemia. This can occur when administering the lidocaine at high doses, typically more than 4-5mg/kg bodyweight for local anesthesia or plasma levels > 5mg/L.

[0032] By administering the lidocaine subcutaneously, oromucosally or sublingually, absorption mainly take place by the lymphatic system, and not the venous system. This avoids toxic plasma levels and hepatic first pass elimination, resulting in low plasma levels of lidocaine, thereby avoiding methemoglobinemia.

[0033] Finding an effective dose without causing toxicity was essential.

[0034] To achieve an IC50 for blocking the P2X7receptor, a plasma concentration of 0.3mM (66.07 ug/ml) is required. By contrast, the maximum tolerable plasma concentration of lidocaine in human is 0.02 mM (4.7 ug/ml), above this level lidocaine will become toxic. This leads to the conclusion that an inhibitory effect on the P2X7 receptor of at least 50% cannot be reached by administering lidocaine using the traditional intravenous route.

[0035] To solve this problem, Applicant formulated lidocaine in a high dose/ low volume solution for subcutaneous, oromucosal or sublingual administration. The sublingual mucosa is known for its high permeability (20 times more absorption speed compered to

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human skin) and additionally, the floor of the mouth and oral cavity has a high concentration of lymph nodes, with makes it perfect for targeting the lymphatic system and immune system.

[0036] An effective adult unit dose of lidocaine, delivered, for example, oromucosally or sublingually, was found to be between 60-100mg, delivered 4-6 times a day. The objective was to provide an effective dose of lidocaine in the plasma of <4.7 µg/ml.

[0037] To prove the suitability of such a delivery method the initial formulation was modified from the Astra Zeneca Xylocaine 10% spray formulation by increasing the concentration of lidocaine from 10 to 25%.

[0038] Rather than deliver a spray, the formulation was delivered from small sealed vials (0.4ml vol) for delivery as drops.

[0039] The formulation, which is significantly more concentrated than current formulations, comprises greater than 10% by volume of lidocaine, and more preferably greater than 20%, and typically 25%. This has the advantage that it avoids a feeling of fullness in the mouth and accompanied hypersalivation, which is poorly tolerated, and which occurs with standard IV formulations (at a concentration of 10%).

[0040] In accordance with a third aspect of the present invention there is provided a method of treating a subject suffering from COVID-19 or an autoimmune disease or a condition in which an immune response caused by the disease or an infection causes a cytokine storm, comprising administering to the subject an effective dose of lidocaine targeted to the lymphatic system, in a suitable dosage form.

[0041] Preferably the lidocaine is administered oromucosally or sublingually.

[0042] Preferably the unit dose comprises from 60-100mg of lidocaine.

[0043] Preferably the unit dose has a volume of less than 0.5ml.

[0044] The treatment may be, the treatment of COVID-19, Acute respiratory distress syndrome (ARDS) or of an autoimmune disease, particularly but not limited to: scleroderma; dermatomyositis; parkinson; and psoriasis.

[0045] Different aspects and embodiments of the invention are further described hereinafter with reference to the detailed description.

DETAILED DESCRIPTION

[0046] The trial formulation is illustrated in Example 1:

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Example 1

Formulation

[0047] Active

- lidocaine: 100mg

[0048] Excipients:

- Lipophilic solvent -levomenthol
- Polar solvent - ethanol 96% 241 mg / ml,
- Co-solvent - polyethylene glycol (Macrogol 400),
- Co-solvent - propylene glycol (E 1520)
- Sweetener - Saccharin (E 954),
- Flavor - banana flavor.
- Diluent - water, purified)
- Total 0.4ml

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[0049] The formulation of the invention was used "off-label" to treat a number of patients to determine its effect as set out in Example 2.

Example 2

Patient trial data

[0050] In the Netherlands, 22 patients were treated as follows:

[0051] 10 patients had COVID-19 symptoms (and were positive and were seen by their general practitioner). All 10 patients presented with early signs of respiratory distress; tachypnoea (more than 30 breaths per minute), high fever and dry cough and a decreased SpO2 < 90. Because they responded well to lidocaine sublingually, they were able to avoid hospitalization for COVID-19);

[0052] 6 patients had post-COVID respiratory complaints. They were experiencing long-term complaints, ranging from coughing, fatigue and shortness of breath to anxiety and physical limitations.

[0053] 6 patients suffered with various autoimmune diseases as follows:

- 1 patient had rheumatoid arthritis.

- 1 patient had scleroderma;
- 1 patient had dermatomyositis;
- 1 patient had morbus Parkinson;
- 2 patients had psoriasis.

[0054] All patients were given the formulation as described in Example 1 above, up to 6 times a day, for up to 2 weeks.

[0055] Out of a total of 22 patients, 8 responded to this treatment within hours, and recovered, without problems, within days.

[0056] The 10 patients with COVID-19, and 6 with post-COVID respiratory complaints had fully recovered within two weeks.

[0057] 5 of the 6 patients with the identified autoimmune diseases experienced significant improvement after 2 weeks of treatment and all had no side effects.

[0058] Only 1 patient showed minimal improvement, and that was a 56 years old male patient with severe chronic rheumatoid arthritis.

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Conclusion

[0059] Administration of lidocaine, targeting a subject's lymphatic system, appears effective in treating COVID-19. The sublingual/ oromucosal approach is a simple, effective, non-invasive approach. A high concentration dose of greater than 10% lidocaine in a small volume, less than 0.5m is optimal.

CLAIMS

1. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS), wherein the Lidocaine or a salt thereof is formulated with a lipophilic excipient for subcutaneous, oromucosal or sublingual delivery, to target the lymphatic system, and comprises a unit dose of from 40-100mg of lidocaine or a salt thereof in a volume of less than or equal to 0.5ml.
2. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in claim 1 wherein the lipophilic excipient is menthol.
3. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in claim 1 or 2 further comprising a polar solvent.
4. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in claim 3 wherein the polar solvent is ethanol.
5. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in any of the preceding claims further comprising one or more co-solvents.
6. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in claim 5 wherein the one or more co-solvents comprise polyethylene and polypropylene glycol.
7. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in any of the preceding claims further comprising a sweetener and a flavourant.
8. Lidocaine or a salt thereof for use in the treatment of COVID-19 or Acute respiratory distress syndrome (ARDS) as claimed in any of the preceding claims further comprising at least a 20% by weight solution of lidocaine or a salt thereof.

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