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(54) Title: COMPOSITION CONTAINING OPIOID ANTAGONISTS AND SPRAY DISPENSER

(57) Abstract

A spray applicator is disclosed for administering an opioid antagonist selected from naloxone and/or naltrexone. The applicator is capable of delivering single or multiple doses of the antagonist through a projecting delivery portion which is shaped or dimensioned for introduction into the nose or mouth. A pharmaceutical composition for nasal or oral administration is also disclosed which comprises an opioid antagonist, such as naloxone and/or naltrexone, and which comprises a water–susceptible solid carrier admixed with the opioid antagonist.

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# COMPOSITION CONTAINING OPIOID ANTAGONISTS AND SPRAY DISPENSER

This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage.

Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation.

The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage.

According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient.

According to another aspect of the invention there is provided a pharmaceutical composition for oral or nasal administration comprising an opioid antagonist, the composition being in finely-divided solid form and comprising a water-susceptible solid carrier and the opioid antagonist.

The spray applicator may be designed for dispensing the solution into the mouth, e.g. sub-lingually, and be provided with a projecting delivery portion for this purpose. However, in a preferred embodiment, the applicator has a delivery portion which is shaped and dimensioned for introduction into a nostril so that the dose is sprayed directly into the nasal passages. The latter mention of administration may be more convenient and enables resuscitation to be continuously and simultaneously applied. Also, a device which has such a projecting delivery portion can also, if appropriate, be applied directly into the mouth.

Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle.

According to the aspect of the invention in which the pharmaceutical composition is in powder form, it is preferably administered nasally. In this embodiment, the composition is packaged via a dispenser having a projecting portion for introduction into a nostril. Normally, a propellant is employed for generating an aerosol of the powdered pharmaceutical in a stream of gas. The dispenser will generally include means for metering doses of the composition dispensed into the patient's nasal passages.

A preferred opioid antagonist for use in the compositions of this invention is naloxone, which is:-

17-allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine.

Another example of an opioid antagonist is naltrexone, which is:-

17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

A mixture of two or more opioid antagonists may be employed. Preferably, naloxone is used as a sprayable liquid composition and naltrexone is preferably used in the form of a powdered, solid composition, usually for nasal administration.

Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution. A concentration of about 0.9 weight/volume NaCl in purified water is suitable. The composition may include a buffering agent to maintain the opioid in solution in the salt form, e.g. a phosphate buffer, such as sodium hydrogen phosphate to maintain the solution at a slightly acid pH. A solution of the antagonist, usually in the form of the hydrochloride, at a concentration of from about 0.5 to 5% by weight, preferably about 1 to 2%, may be employed for nasal or buccal administration. The

liquid composition may be packaged in a metered dosage spray dispenser, using a pump or propellant. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µl and 100µl, with the dose per shot preferably varying between 200 and 1200µg.

In the case of a solid, powdered composition for nasal administration, the antagonist is mixed with one or more solid, powdered carriers. Suitable carriers include saccharides such as sorbitol, mannitol, lactose, fructose, glucose and sucrose. Other carriers include water-soluble or swellable polymers such as cellulose derivatives, for example, hydroxypropyl methyl cellulose and carboxymethyl cellulose. A solid salt of the antagonist, e.g. the hydrochloride, maybe mixed with a carrier, or coated with the carrier or with a third material such as a hydrophilic polymer.

Solid, powdered formulations generally are dispensed at a total shot weight of about 20mg, giving a naloxone dose of 400µg per shot. Typical total shot weights may vary between about 10 mg and 30mg and the naloxone dose per shot may be between about 200 and 1200µg.

The solid, powdered composition containing the opioid antagonist may be packaged in a dispenser with a suitable propellant, such as HFC-134a or HFC-227. Again, a valve may be provided, which is adapted to dispense a dosage unit of the antagonist of about 0.2 to 5 mg, e.g. 0.4 to 2mg preferably 0.4 to 1.2mg.

It may be desirable to include an anti-oxidant, such as ascorbic acid or citric acid in the powdered formulation.

The invention is illustrated by the following Examples of pharmaceutical compositions suitable for use in dispensing the opioid antagonist and by the accompanying drawing and description of one form of spray applicator suitable for dispensing the liquid composition.

**Example 1**

Sprayable aqueous liquid composition for a nasal applicator.

Naloxone hydrochloride was dissolved in a solution of purified water to form a solution containing 0.8% weight/volume of the naloxone. Benzalkonium chloride was

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