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Intravenous Formulation of Solithromycin, a Painless Macrolide Antibiotic in a Rabbit Intravenous Injection Model

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Abstract

Background: Solithromycin is a potent new fluoroketolide in development for treatment of bacterial respiratory tract and other infections. Solithromycin is currently in Phase II trials for the oral dosage form and Phase I trials for the IV dosage form. Historically, macrolide antibiotics, such as clarithromycin and erythromycin, are known to cause pharmacologically-related pain with IV injection. Solithromycin is the first macrolide since azithromycin to have the potential for an IV formulation, allowing for clinical trials in moderately severe to severe community-acquired bacterial pneumonia. In this study, solithromycin IV formulations were evaluated for pain upon injection, using the rabbit ear vein model, and compared to Azithromycin for Injection.

Methods: (i) Single dose studies: 5 ml of solithromycin IV formulations at 2 and 3 mg/ml were infused into rabbit ear veins at 1, 2, 3, and 4 ml/min. 5 ml of azithromycin (2 mg/ml) was infused at 4 ml/min. **(ii)** Multiple dose study: 5 ml of IV solithromycin was infused at 2 concentrations (2 and 3 mg/ml) at 3 ml/min daily for 5 days, with a control group receiving vehicle only.

Results: In the single dose study, rabbits did not show any pain with solithromycin IV formulations of 2 mg/ml or 3 mg/ml at infusion rates up to 4 ml/min. In contrast, rabbits injected with azithromycin IV solution experienced strong movements of ear, head, and body, with vocalization upon administration, and were removed from the study. In the multiple dose study, rabbits infused with solithromycin did not show any signs of pain for up to 5 days, though some injection site irritation was noted on Days 4-5, probably due to the mechanical irritation of repeated injections. Rabbits infused with the formulation vehicle also experienced similar injection site irritation.

Conclusion: Solithromycin IV formulations did not cause any pain in the single or multiple dose studies using the rabbit ear vein model. In contrast, Azithromycin for Injection caused a high degree of pain as a single dose at the concentration and infusion rate approved for hospital administration.

Introduction

CEM-101 (Solithromycin), a potent new fluoroketolide in development for treatment of bacterial respiratory tract and other infections (1, 2). Intravenous toxicology was conducted in dogs and monkeys by once a day injection, daily for 28 days. At doses of 15 mg/kg in the dog and 25 mg/kg in the monkey the intravenous dosing was well tolerated and achieved C_{max} values of 3.9 µg/ml in the dog and 5.9 µg/ml in the monkey (3) . Nausea and vomiting, but not pain, were the dose limiting toxicity in these studies. CEM-101 has completed Phase II trials for the oral dosage form for Community Acquired Bacteria Pneumonia (CABP) and the Phase I trials for the IV dosage form are currently running. The IV formulation of solithromycin will allow for clinical trials in moderately severe to severe CABP.

Macrolides are known to produce pain on injection. Intravenous formulations of approved macrolides including azithromycin, clarithromycin and erythromycin cause pain upon injection (the IV formulation of clarithromycin is not approved in the US) (4, 5, 6). This pain can be pharmacological in nature or can be due to the poor solubility of macrolides leading to vein irritation upon infusion.

In this study, solithromycin IV formulations were evaluated for pain upon injection using the rabbit ear vein model. Azithromycin for Injection was used as the comparator.

Materials and Methods

- Rabbit, New Zealand White, female, 2.5-3.2 kg
- Solithromycin drug product, Cempra Pharmaceuticals
- Solithromycin infusion solution buffer, Cempra Pharmaceuticals
- Azithromycin Citrate, Azithromycin for Injection, PLIVA
- Half normal saline

Solithromycin drug product was reconstituted and diluted into its IV injection solution at 2 mg/ml and 3 mg/ml.

Azithromycin was reconstituted and diluted in half normal saline at 2 mg/ml.

	Concentration of Solithromycin	Injection Rate	Injection volume	Azithromycin concentration and infusion rate	Control	Number of Rabbits
Single Dose	2 mg/ml 3 mg/ml	1, 2, 3, 4, ml/min	5 ml	2 mg/ml at 4 ml/min	Injection vehicle	2 rabbits for each formulation
Multiple Dose (for 5 days)	2 mg/ml	3 ml/min	5 ml	NA	Injection vehicle	1 rabbit each for the control and solithromycin

The animals were observed during and up to 30 minutes post-infusion and reactions were recorded.

Reactions were scored in the single dose study according to modified Draize Score.

Modified Draize Score:

0	1	2	3	4
no reaction	slight twitch of the ear	ear twitch and head movement	strong head movement	strong movement of ear, head, body and vocalization

Results

Single Dose using Modified Draize Score

Azithromycin Citrate in Half Normal Saline

Animal ID	Half normal saline at 4 ml/min	Azithromycin (2 mg/ml) in half normal saline at 4 ml/min
1	0	4 (strong ear, head and body movement with vocalization)
2	0	4 (strong ear, head and body movement with vocalization)

Solithromycin IV Infusion Solution

Animal ID	Vehicle at 4 ml/min	Solithromycin (2 mg/ml)				Solithromycin (3 mg/ml)			
		1 ml/min	2 ml/min	3 ml/min	4 ml/min	1 ml/min	2 ml/min	3 ml/min	4 ml/min
5	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0

Multiple Dose

Solithromycin IV Infusion Solution

Animal ID	Vehicle at 3 ml/min	Solithromycin (2 mg/ml) at 3 ml/min
Day 1	No reactions	No reactions
Day 2	No reactions	No reactions
Day 3	No reactions	No reactions
Day 4	Irritation around needle stick - no reaction distal to needle	Irritation around needle stick - no reaction distal to needle
Day 5	Irritation around needle stick - no reaction distal to needle	Irritation around needle stick - no reaction distal to needle

Conclusions

- In the single dose study, rabbits did not show any pain with solithromycin IV formulations of 2 mg/ml or 3 mg/ml at infusion rates up to 4 ml/min. In contrast, rabbits injected with azithromycin IV solution (at the concentration and infusion rate approved for hospital administration) experienced strong movements of ear, head, and body, with vocalization upon administration.
- In the multiple dose study, rabbits infused with solithromycin did not show any signs of pain for up to 5 days, though some injection site irritation was noted on Days 4-5, probably due to the mechanical irritation of repeated injections. Rabbits infused with the formulation vehicle also experienced similar injection site irritation. Azithromycin was not tested in the multi dose arm because of the strong pain response in the single dose study.
- The IV formulation of solithromycin that was used to successfully complete 28-day toxicology studies in dogs and monkeys is currently in phase I clinical trials (3).

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