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Summary: *This study tested the iPRECIO® pump in a chronic subcutaneous angiotensin II infusion protocol run in conscious adult rats to produce chronic hypertension. This protocol has been very reproducible when using an implantable osmotic pump, representing an excellent modality for comparing the function of iPRECIO to existing technology. Both pump types led to the expected hypertension with the iPRECIO pump initiating hypertension more rapidly, and maintaining a higher level of arterial pressure. iPRECIO proved reliable and easy to use and data suggests iPRECIO is more efficient than osmotic pumps and is well tolerated in chronic study.*

Introduction

Systemic arterial hypertension is a global concern. Animal models of hypertension are well characterized and the rat has become a standard model used to identify physiological mechanisms that either contribute to or result from the development of hypertension. A major focus of the Fink lab is studying the pathology of hypertension, specifically how sympathetic nerves affect regulation of the cardiovascular system. A hypertension model used and replicated consistently in this and other labs is a chronic angiotensin II infusion model that focuses on how the hormone angiotensin II influences sympathetic nerve function. The ultimate goal of the Fink lab is to use novel models to develop new therapeutic approaches to cardiovascular disease.

This study tested the iPRECIO® pump in a chronic subcutaneous infusion protocol in which angiotensin II was administered over 14 days in conscious adult rats to produce chronic hypertension. As mentioned, this protocol has been performed extensively using an implantable osmotic pump, representing an excellent modality for comparing the function of iPRECIO to existing technology with known outcomes. At the conclusion of the iPRECIO study it was evident that both pump types led to the expected hypertension with the iPRECIO pump initiating hypertension more rapidly, and maintaining a higher level of arterial pressure. iPRECIO proved reliable and easy to use



and data suggests iPRECIO is more efficient than osmotic pumps and is well tolerated in a chronic study.

Materials and Methods:

This protocol examined 1) the reliability and durability of the iPRECIO pump when implanted for a continuous infusion of up to 4 weeks, 2) the ease and dependability of multiple refilling of the pump transcutaneously.

The study was conducted in seven Sprague Dawley rats weighing 300-325 grams. Radiotelemetry transmitters

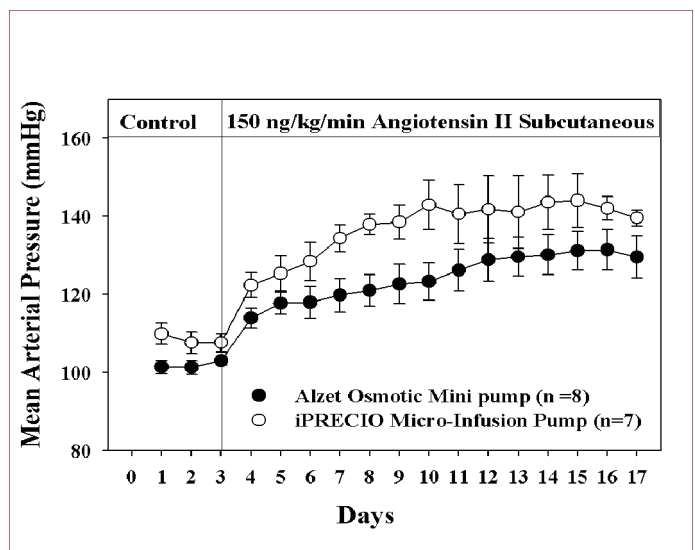


Figure 1: Subcutaneous infusion of angiotensin II by both pumps led to the expected development of chronic hypertension. The iPRECIO pump appeared to initiate hypertension more rapidly, and maintain a higher level of arterial pressure than the Alzet pump.

(PA-C40, DSI) for measuring arterial pressure were implanted in all rats. After a 3-day control period, iPRECIO micro-infusion pumps were implanted in all rats. All pumps were filled with angiotensin II to produce an infusion rate of 150 ng/mg/min subcutaneously. Previously obtained data from the Fink laboratory using the Alzet mini-osmotic pump were used for comparison purposes.

Surgical Procedures:

Radiotelemetry implantation

Under general anesthesia, the tip of the transmitter catheter was inserted into the abdominal aorta by way of the femoral artery. The body of the transmitter was placed in a subcutaneous pocket along the abdomen. All incisions were closed in layers. All animals were given 7 days to recover. Rats were housed in individual Plexiglas® cages and placed on radiotelemetry receivers (RPC-1, DSI). The arterial blood pressure was recorded for 10 seconds every 10 minutes throughout the experiment. A commercially available radiotelemetry data acquisition program (Dataquest, DSI) was used to remotely monitor the arterial pressure.

iPRECIO micro-infusion pump implantation

After the 3 day control period, a medial dorsal incision below the scapula was made and a pocket created for the iPRECIO micro-infusion pump. The pump, which was filled with angiotensin II, was sutured in place to surrounding muscle. A separate pocket was created for the

catheter attached to the pump. This was done so that infusate would not pool around the infusion pump. All incisions were sutured closed. Each pump was individually assigned to a rat and programmed into the iPRECIO management software for the *Instant* infusion mode at a set infusion rate of 5.0 ul/hr. Refill dates and volumes were strictly adhered to throughout the study.

Results:

Subcutaneous infusion of angiotensin II by the iPRECIO pumps led to the expected development of chronic hypertension. The iPRECIO pump appeared to initiate hypertension more rapidly and maintained a higher level of arterial pressure than the osmotic pump (figure 1). The osmotic pump could only be used for 14 days. The iPRECIO pump, after transcutaneous refills, maintained an elevated level of arterial pressure for four weeks of continuous infusion (figure 2). No difficulties were experienced with filling the pumps and the rats tolerated the pump's presence well.

Discussion

The iPRECIO micro-infusion pump is reliable and easy to use. Efficiency of the iPRECIO pump appears to exceed that of osmotic pumps, based on the level of blood pressure produced during Angiotensin II infusion. The pumps are well-tolerated for long periods of time (at least a month) by rats weighing at least 300g.

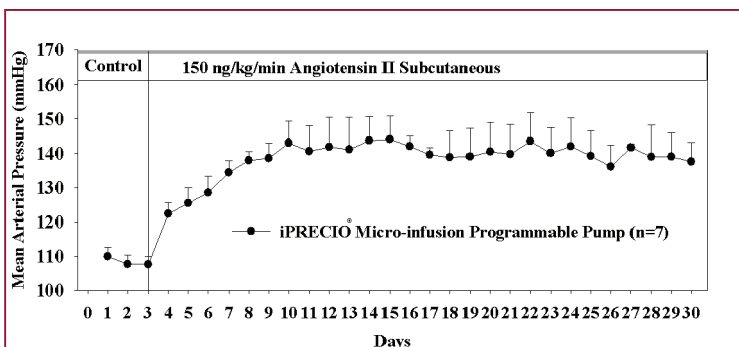


Figure 2: The Alzet pump could only be used for 14 days. The iPRECIO pump, after transcutaneous refills, maintained an elevated level of arterial pressure for 4 weeks of continuous infusion.