

# TELEMETRY IN THE GUINEA-PIG : A MODEL FOR EARLY SAFETY EVALUATION OF HAEMODYNAMIC AND ELECTROCARDIOGRAPHIC PARAMETERS

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## Introduction

The guinea-pig (GP) recently emerged as a species possessing a good predictive value, in particular to evaluate the potential for delayed ventricular repolarization. The technique of radiotelemetry enables in conscious freely moving animals the measurement of both electrophysiological (via the ECG) and haemodynamic (via arterial blood pressure) cardiovascular function. This technique is routinely performed in rats and we aimed to develop a surgical approach for radiotelemetry in guinea pigs, allowing continuous recording of blood pressure, heart rate and ECG for long-term period of time.  
The goal of this work was then to evaluate the effects of a series of compounds, possessing different cardiovascular profiles.

## Methods

- Male Dunkin-Hartley guinea-pigs weighing 250-450g.
- Surgery under isoflurane anaesthesia
- A telemetric radiotransmitter (TL11M2-C50-PXT, Data Science International, Minnesota, USA) for measurements of arterial blood pressure, temperature and ECG was implanted on the back of the neck.
- A small incision was made in the front of the neck to allow access to carotid artery.
- The blood pressure catheter and ECG leads (lead II) were tunneled around to the small incision at the front of the neck where the blood pressure catheter was introduced into the carotid artery and secured in place following closure of the distal end. The ECG leads were tunneled subcutaneously and fixed on the right shoulder and the lower thorax.
- Arterial blood pressure and ECG signals were monitored and stored on the hard disk of a compatible personal computer using Dataquest™ ART™ software.
- Analgesia: buprenorphine 0.05 mg/kg s.c.
- Antibiotic: enrofloxacin 10 mg/kg s.c.
- At least 10 days of recovery

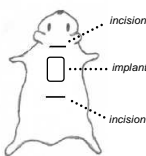


Fig. 1. Schematic diagram of double subcutaneous incision. Incision site for double incision subcutaneous on the back of the animal (according to Provan *et al.*)

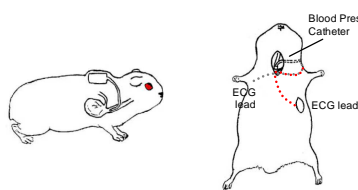
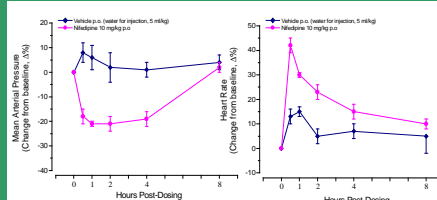


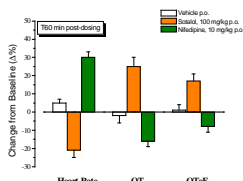
Fig. 2. Schematic diagram of subcutaneous implantation. Subcutaneous implantation showing placement of the ECG in a lead II position and the site of subcutaneous implantation of the body of the implant

## Experimental protocol

- A series of 4 early program compounds (NS-A, NS-B, NS-C and NS-D) were tested in the model after a single oral administration and hemodynamic parameters were monitored over 24h (n=4).
- Satellite GP were used to evaluate drug plasma concentration over a 6-h period after oral dosing (n=3).
- Sotalol and Nifedipine were used for pharmacological validation.

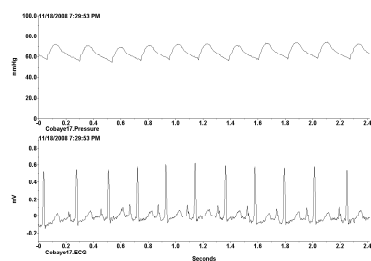


## Pharmacological validation

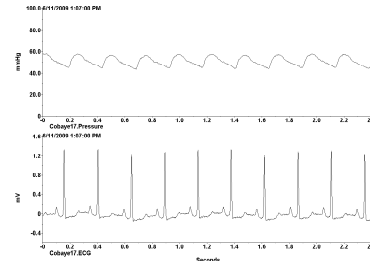


## Arterial pressure and ECG recording

### 1 month post surgery

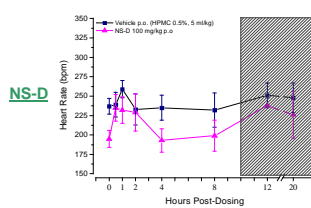
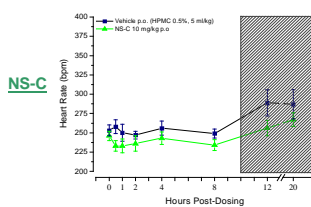
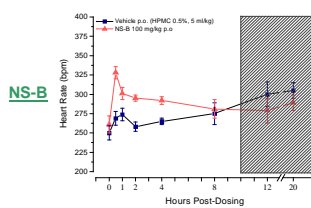
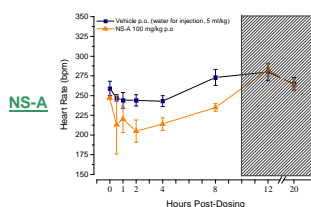


### 8 months post surgery

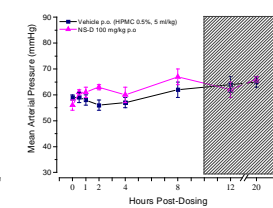
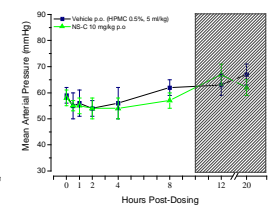
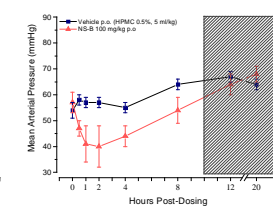
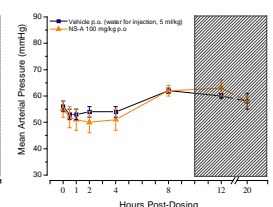


## Results

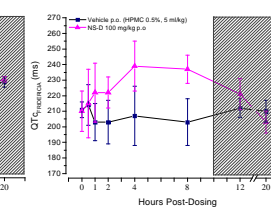
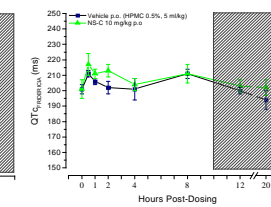
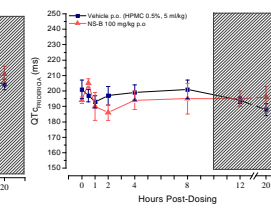
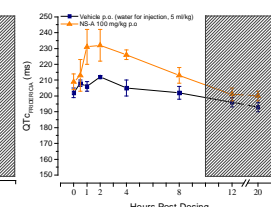
### HEART RATE



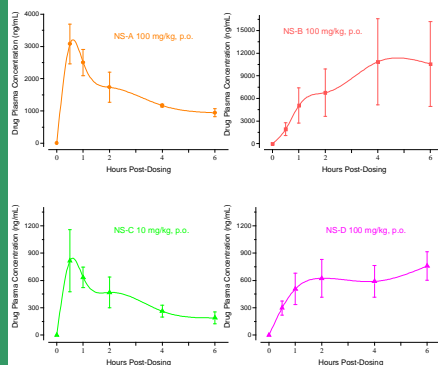
### MEAN ARTERIAL PRESSURE



### QTc FRIDERICIA



## Drug plasma concentration



## Summary and Conclusion

NS-A had no effects on AP but decreased HR and increased both QT and QTc.

NS-B induced a marked decrease in AP associated with a reflex tachycardia but had no effects on QTc.

NS-C had no effects on AP, HR or QTc.

NS-D had no effects on AP but increased HR, QT and QTc.

The results show that this model of telemetry in the guinea-pig, where both electrocardiographic and haemodynamic cardiovascular function are evaluated, is appropriate for early de-risking strategy in drug discovery, according to ICH S7A and S7B guidelines.

## Reference

1. PROVAN *et al.* (2005), *JPTM*, **52**: 223-228
2. FRIDERICIA, (1920), *Acta Med. Scan.*, **53**: 469-486