

Evaluating the dose-response relationship of furosemide on diuresis and RAAS activation in dogs combining multiple comparisons and modeling techniques

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Background

- Situation:** While furosemide provides an overt clinical benefit in **reducing fluid retention** in heart failure (HF) dogs, it also activates the **renin-angiotensin aldosterone system (RAAS)**, which further contributes to the accelerated **progression of the disease**
- Opportunity:** Knowledge on the **dose-response** relationship of furosemide provides a scientific rationale to support **efficacious and safe dosing** of diuretics in HF patients

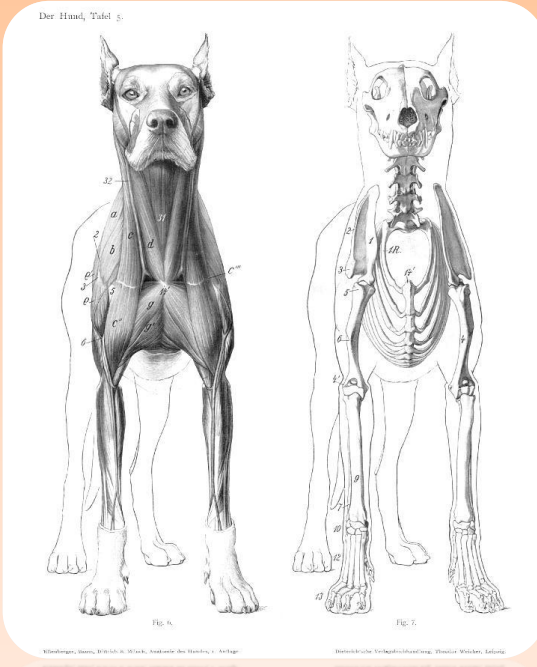
Objectives

- Quantify** and **compare** the **effect** of several increasing doses of **furosemide** on **diuresis**, **renin** activity (RA) and **aldosterone** (AL) in dogs, using a combined **multiple comparisons** and **model-based** approach: MCP-Mod ^[1]
- Predict the **expected response** to furosemide at doses recommended by the American College of **Vet. Internal Medicine (ACVIM)** guidelines^(§) ^[2]
(§)The specific dosing of furosemide in CHF dogs should be related to the severity of clinical signs and the response to initial therapy i.e.1–4 mg/kg q12h

Methods

- 24 healthy beagle dogs were allocated to 4 treatment groups (saline control, furosemide 1, 2, and 4 mg/kg I.M., q12h for 5 days)
- RA** and **AL** **trough** values, and **24-hour diuresis** after the last administration day were analyzed at **steady state** using **MCP-Mod**
- A **model averaging** technique was used to derive the **dose-response** curve for each endpoint of interest

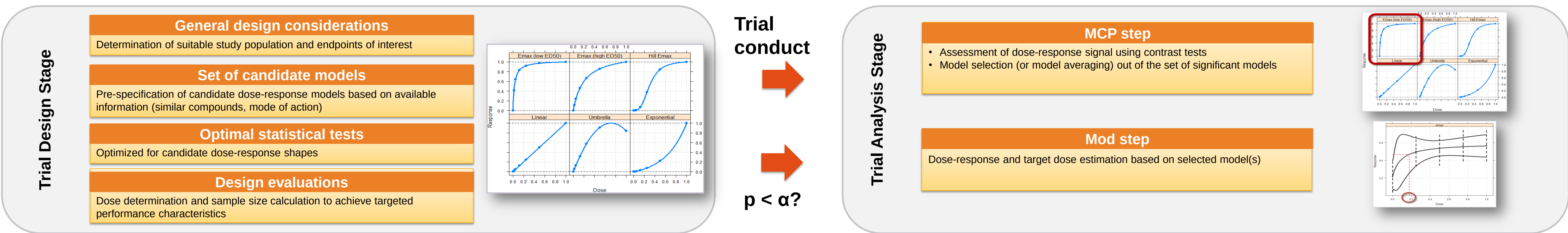
Conclusion and Perspectives



- MCP-Mod is a **powerful** tool for **evaluating multiple dose-responses** in **veterinary pharmacology**
- Our data show that **furosemide** produces a **sub-maximal effect** on **diuresis** at **doses lower** than those identified to **activate the systemic RAAS**
- Predictions from the model-based approach confirm that **doses recommended** by the **ACVIM guidelines** are **efficacious** on diuresis
- Doses **lower than 1 mg/kg q12h** should produce a significant **effect** on **diuresis**, with only **mild activation** of the RAAS

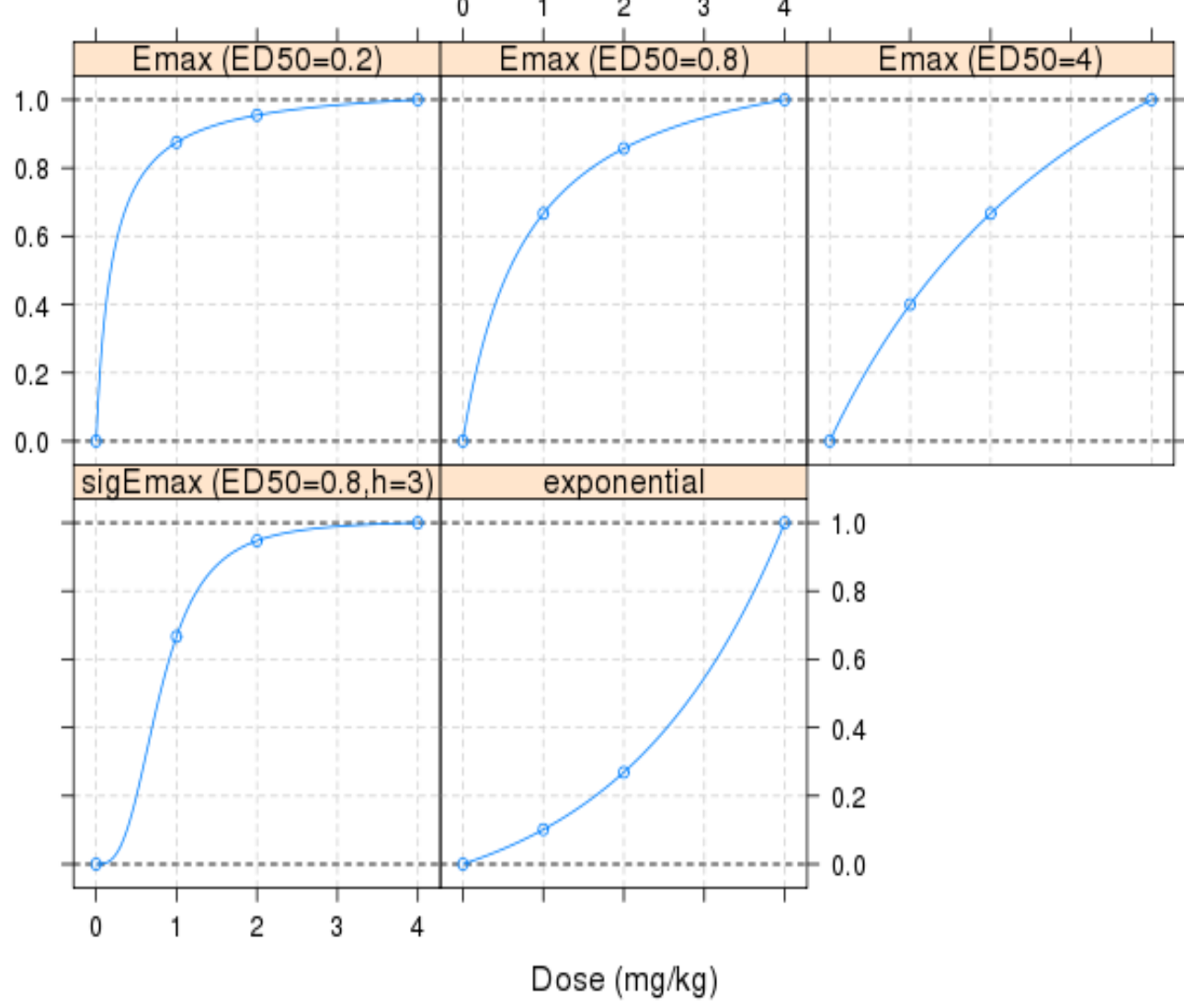
A word on MCP-Mod

- At the **trial design stage**, a suitable set of candidate models is identified in clinical team discussions, which also impacts decisions on the number of doses, required sample sizes, and patient allocations
- At the **trial analysis stage**, the dose-response is tested using trend tests based on the candidate models. Once a dose-response signal is established, the best model or a weighted average of models out of the set of candidates is then used for estimation of dose-response and target dose ranges



Results

Figure 1. Set of dose-response candidate models



The **candidate set** of dose-response models was selected based on **available literature** in dogs^[3] (Figure 1). The dose response modeling was performed on the **averaging** of 5 models

The MCP-Mod analysis **captured** reasonably **well** the **dose-response relationship** for all endpoints of interest over the investigated dose-range (Figure 2)

The **EDs** estimates were relatively **consistent** across all **RAAS endpoints** (RA and AL) and seemingly **greater** than those for **diuresis** (Table 1)

Based on the study results, doses **lower than 1 mg/kg q12h** are expected to be efficacious on **diuresis**, while producing **mild activation** of RA and AL (Table 2)

Table 1. Model estimated parameters

Parameters	Endpoint	Estimate	80% Confidence Interval	
ED20 (mg/kg)	Plasma AL	0.55	0.21	0.73
	Plasma RA	0.60	0.37	0.70
	24-hour diuresis	0.29	0.01	0.49
ED50 (mg/kg)	Plasma AL	0.93	0.56	1.60
	Plasma RA	0.91	0.71	1.08
	24-hour diuresis	0.52	0.01	0.77
ED80 (mg/kg)	Plasma AL	1.55	1.06	5.59
	Plasma RA	1.41	1.13	2.81
	24-hour diuresis	0.93	0.01	1.66
Emax (mg/kg)	Plasma AL	1118	893	1593
	Plasma RA	7459	6641	8783
	24-hour diuresis	943	834	1093

Figure 2. MCP-Mod dose response curves estimates

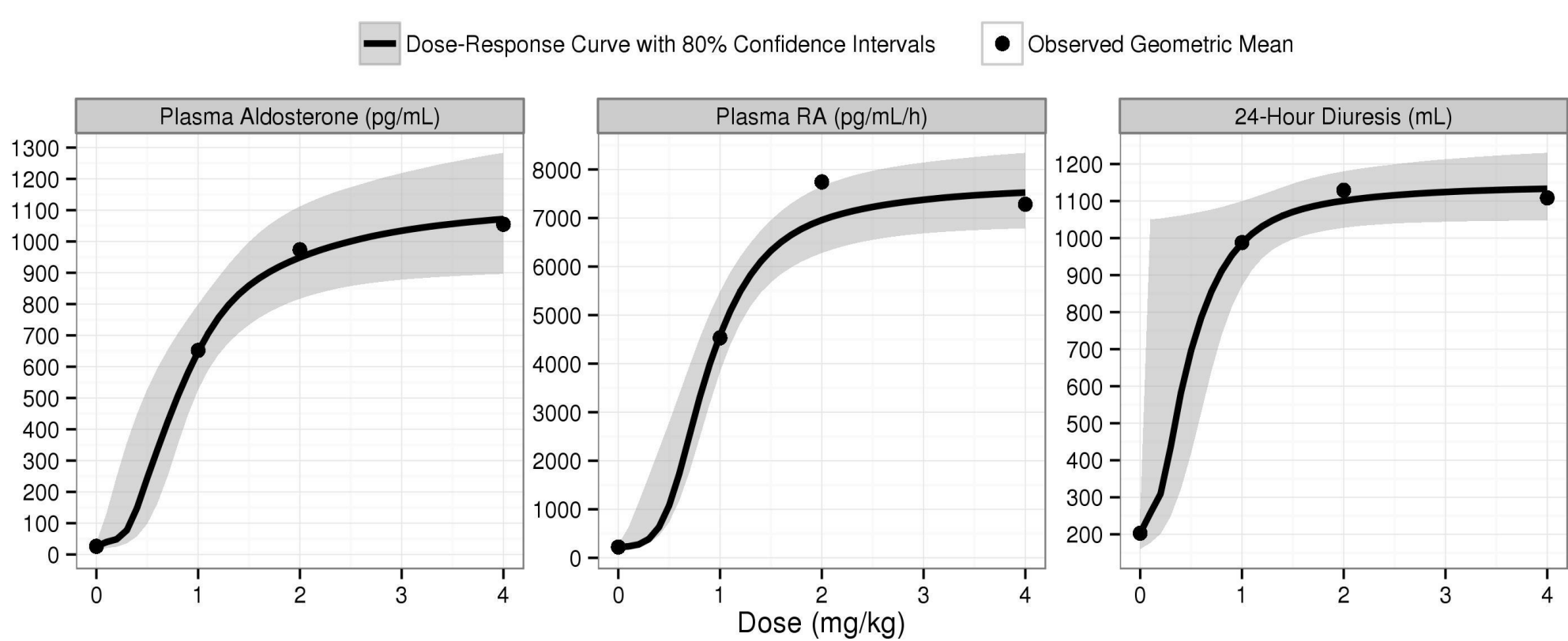


Table 2. Point estimates (absolute and % of maximum)

Endpoint	Dose (mg/kg)	Estimate (Absolute)	Estimate (% of Maximum)
Plasma AL (pg/mL)	0	26	0
	1	648	55
	2	949	89
	4	1072	99
Plasma RA (pg/mL/h)	0	222	0
	1	4586	58
	2	6958	92
	4	7524	99
24-hour diuresis (mL)	0	203	0
	1	987	83
	2	1101	97
	4	1133	99

References: [1] Bretz F, Pinheiro JC, Branson M. Biometrics, 61:738–748 (2005)
[2] Atkins C, Bonagura J, Ettinger S et al. J Vet Intern Med, 23:1142-50 (2009)
[3] Klatt P, Muschawek R, Bossaller W et al. J Vet Res, 36(7):919-923 (1975)

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