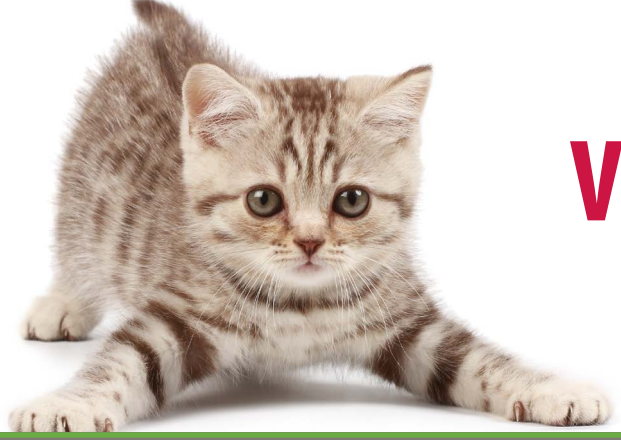

Vetnostics Newsletter

October 2018

Full Day Clinical Pathology Workshop: Thursday 14th March 2019

Do you perform in-house pathology?

Do you want to improve your in-house pathology skills?

Left to right: Dr Brett Stone, Dr Kathryn Jenkins, Dr Harold Tvedten, Dr Susan Boyd

Then do not miss this unprecedented opportunity to advance your knowledge and skills in haematology, cytology, urinalysis and biochemistry.

This full day workshop will be held as part of the Veterinary Specialist Services (VSS) 2019 Annual Veterinary Conference in Brisbane. It will be run by four specialist veterinary clinical pathologists including; three TML Vetnostics pathologists **and internationally renowned Clinical Pathologist Dr Harold Tvedten.** This innovative program will encompass hands-on microscopic evaluation, case presentations and case-by-case based result interpretations.

Register via the VSS 2019 Conference website: **www.vssconference.com/copy-of-tickets**

Further details are available at **www.vssconference.com**

Places are strictly limited so please **book early to avoid disappointment**.
Early bird discounted registration expires 14th December 2018.

Electronic Pathology Supplies Ordering is Now Available

Requests for free* pathology supplies can now be submitted electronically via the TML Pathology Vetnostics website:

Please ensure to follow the specific instructions below when submitting pathology supplies orders electronically.

1. Download Acrobat Reader 

2. Download the 'Vet Supply Requisition Form' located at;
   http://www.tmlpath.com.au/Portals/0/PDF/Vetnostics/615_T_VetSupplyForm_Jun18.pdf.
3. Open downloaded form using Acrobat Reader (note: the submit button on the form won't work in your browser's default PDF viewer)
4. Complete form
5. Click the 'submit' button on the form

*: These pathology collection items are supplied at no charge for submission of samples to QML Pathology Vetnostics. Quantities supplied will be limited by usual number of submissions.

SDMA (symmetric dimethylarginine) Best Practice Statement

BACKGROUND

Serum SDMA is a surrogate marker of reduced GFR, similar to creatinine[1]. As with any marker of GFR, elevated SDMA is not specific for renal disease but may also be due to pre-renal factors (e.g. dehydration, shock and hypoadrenocorticism) or post-renal factors.

- In acute kidney injury (AKI), SDMA provides no diagnostic advantage or additional information over creatinine[2].
- **False Negatives:** In chronic kidney disease (CKD), serum SDMA increases earlier than serum creatinine in some **(but not all)** dogs and cats. However, in a subset of animals SDMA increases later than creatinine[2]. Furthermore, there are confirmed cases of IRIS stage 3 renal failure where SDMA has been normal[2]. The reasons for such large discrepancies are as yet unknown. However, there is mounting evidence that SDMA is also affected by non-renal factors[4].
- **False Positives:** Elevated serum SDMA results (results above reference range) will occur in clinically normal animals (especially in young to middle aged cats and most dogs) without azotaemia or clinical evidence of renal disease.
  - In cats, specificity of SDMA in detecting CKD has been reported as 91%[3]. On this basis, in a low disease prevalence population (e.g. reported prevalence of CKD is < 5% in cats < 10 years of age), **more than 60% of positive SDMA results will be false positives** if the test is applied in an indiscriminate fashion.
  - In dogs, specificity of SDMA in detecting CKD has been reported as 68%[6]. Based on reported prevalence of CKD (< 4% in the general canine population across all ages[5]), **around 90% of positive SDMA results will be false positives** if the test is applied in an indiscriminate fashion.
- In azotaemic animals with normal muscle mass, SDMA appears to provide no diagnostic advantage or additional information over elevated creatinine[2].

VETNOSTICS SDMA EVIDENCE-BASED SUMMARY AND RECOMMENDATIONS:

- SDMA should not be run indiscriminately in routine biochemistry profiles, particularly in clinically healthy young to middle aged cats and most dogs of any age (due to potential for false positives).
- In azotaemic dogs and cats with normal muscle mass, SDMA appears to provide no diagnostic advantage or additional information over elevated creatinine.
- If acute renal failure is suspected, SDMA provides no diagnostic advantage or additional information over creatinine[1].
- If CKD is suspected in a non-azotaemic animal (e.g. based on age, PU/PD, persistent suboptimal USG, proteinuria, breed, drug therapy) and/or if there is significant muscle wasting, SDMA may be a useful additional test to creatinine for assessment of GFR. Requests for SDMA can be made at the time of initial submission of a routine biochemical profile or added later (i.e. if creatinine is normal).

In those instances where clinical examination and initial biochemistry and urine analysis results indicate that there may be additional value in performing SDMA analysis, samples can be forwarded to IDEXX for SDMA analysis. IDEXX will report and invoice clinics directly.

Selected References

1. **Braff et al.,** Relationship between Serum Symmetric Dimethylarginine Concentration and Glomerular Filtration Rate in Cats. J Vet Intern Med 2014;28:1699–1701.
2. **Dahlem et al.**, Plasma Symmetric Dimethylarginine Concentration in Dogs with Acute Kidney Injury and Chronic Kidney Disease. J Vet Intern Med 2017;31:799–804.
3. **Hall et al.** Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. J Vet Intern Med 2014;28:1676–1683.
4. **Langhorn et al.,** Symetric dimethylarginine in cats with hypertrophic cardiomyopathy and diabetes mellitus. J Vet Intern Med 2017:Open Access DOI: 10.1111/jvim.14902.
5. **O'Neill et al.** Chronic kidney disease in dogs in UK veterinary practices: Prevalence, risk factors, and survival. J Vet Intern Med 2013;27:814–821.
6. **Pelligand et al.,** Early detection of kidney disease in dogs: a comparison of serum SDMA and creatinine versus GFR measured by iohexol clearance. 2017;J Small Anim Pract: Vol 58, Supp1.:8.

SVS Specialist Veterinary Services incorporating

Vetnostics | VETPATH LABORATORY SERVICES | Vetnostics | TMLPathology | ASAP LABORATORY | Vetnostics | QML Pathology

Vetnostics does not recommend the use of "Pre-pill Cortisols" for Trilostane monitoring

Dr Sue Foster. Vetnostics Medical Consultant.

VETNOSTICS RECOMMENDATIONS: SUMMARY

1. Vetnostics believe that pre-pill monitoring cannot be justified based on the scientific evidence available
2. Vetnostics do not recommend pre-pill monitoring.
3. If owners are cost constrained then the options are:
    1. do the 1h post-stimulation cortisol only (to reduce the cortisol costs) in an ACTH stimulation test 4-6h post trilostane
    2. use the minimal amount of ACTH possible (1-5 ug/kg aqueous Synacthen IV if testing at exactly 60 minutes after ACTH) and freeze the remainder in appropriate aliquots (aqueous Synacthen can be stored frozen for 6 months)
    3. change to a cheaper drug with less onerous monitoring, namely mitotane! This is still a very good drug for treating hyperadrenocorticism and actually the preferred treatment of some endocrinologists. We must not forget this very efficacious and long-proven treatment of hyperadrenocorticism.

Recommendations for trilostane monitoring have recently included the possibility of pre-pill cortisol measurement as a replacement for a routine ACTH stimulation test performed at the estimated peak effect of trilostane.

Use of pre-pill cortisol monitoring offers substantial cost benefits, potentially making trilostane treatment more affordable and attractive to clients. Whilst this is an enticing proposition, we need to carefully examine the science behind this recommendation.

Firstly, pre-pill cortisol monitoring entails assessing drug efficacy at a time when the drug's effects are likely to be minimal or negligent and would thus seem to be of questionable logic.

Secondly, it involves measurement of a hormone, well documented for its fluctuations in healthy and diseased dogs and known to range from 1-58 nmol/L (median 21.5 nmol/L) in healthy well conditioned calm dogs (Foster 1998; Foster 2011).

Thirdly, one cannot directly compare cortisol measurements between laboratories and between different cortisol assays (Graham 2017; Macfarlane et al 2016) so using fixed "cortisol" values worldwide is not scientifically valid.

Lastly, the source of the recommendation is one paper (MacFarlane et al 2016) which was funded by Dechra Veterinary Products (UK), the manufacturer of trilostane.

THE "PRE PILL CORTISOL" STUDY

The study was not without limitations including:

1. That dogs with adrenal and pituitary dependent hyperadrenocorticism receiving once or twice daily trilostane were all included as one group
2. That the unvalidated survey used was developed from an "ad hoc survey of practising veterinarians" using an unvalidated weighting of the questions by the authors
3. The authors choice of optimum monitoring test efficacy was then based on a Receiver Operator Characteristic (ROC) curve maximised for specificity of optimal cut-offs to reduce the likelihood of unnecessary dose increases, potentially favouring less rigid control of hyperadrenocorticism and less cost for owners
4. The study used ACTH stimulation testing performed 3 hours after trilostane dosing, based on a pilot study by Griebsch et al (2014). This study assessed basal cortisol measurements in 9 dogs (not post ACTH stimulation cortisol measurements). Data was not normally distributed and the graphical representation of geometric data (mean and dispersion factor) demonstrated considerable overlap at most time points. Thus 3h post-trilostane ACTH stimulation testing itself is questionable, especially given the peak effect variability demonstrated so neatly in another study (Bonadio et al 2014). The authors failed to acknowledge the possibility that the reason why measurement of post-stimulation cortisol 3h after trilostane dosing was not useful, was that it may not have been the optimal time for testing for trilostane efficacy.
5. Dogs with excellent control of hyperadrenocorticism in the study actually had a median ACTH -stimulated cortisol of approximately 60-70 nmol/L (extrapolated from the box and whisker plot of Figure 1 in the paper) not 130 nmol/L, the figure used as a cutoff in the ROC curve. Using the Centaur Advia assay at Vetnostics (not directly comparable), a post-stimulation cortisol of 60-70 (in an ACTH stimulation test performed 4-6h after trilostane) would be associated with good control and a post-stimulation result of 130 nmol/L would be associated with poor control of hyperadrenocorticism.

The upshot, with these limitations, was that pre-pill cortisol measurement performed better than an ACTH-stimulated cortisol of 130 nmol/L in an ACTH stimulation test performed 3 hours after trilostane.

>>> CONTINUED OVERLEAF

Whilst the study was interesting, some of the limitations (including difficulty of extrapolation of these results to other laboratories and other assays) were actually acknowledged by the authors and it should have been regarded essentially as a pilot study. Instead, pre-pill cortisol monitoring was almost immediately endorsed by the European Society of Veterinary Endocrinology in a Consensus Statement. The survey questionnaire for this Consensus Statement required assessment of seven separate statements regarding hyperadrenocorticism and cortisol measurement, a number of which would be unarguable, but one at least was quite controversial (pre pill cortisol monitoring). Survey participants then only had 2 options: "endorse" or "absolutely cannot endorse" the Consensus Statement in its entirety. It is possible (perhaps likely) that participants who agreed with 5/7 or 6/7 statements may not have chosen "absolutely cannot endorse" based on objections to only one or two statements.

A study presented as an abstract after the ESVE Consensus Statement (Sieber-Ruckstuhl et al 2017), compared two pre-pill cortisol measurements in trilostane-treated hyperadrenococorticoid dogs and found 30% disagreement in cortisol measurements taken one hour apart. The presenter (Sieber-Ruckstuhl) stated that both cortisol measurements were susceptible to stress, and that stress was difficult to define or assess in individual dogs. Despite this, the authors of this study appeared to also support pre-pill monitoring. Their study also received funding from Dechra Veterinary Products (UK).

After these studies, pre-pill cortisol monitoring was then incorporated into the monitoring recommendations of Dechra Veterinary Products (UK) using information from both studies. Interestingly, whilst the recommendations do incorporate the pre-pill cortisol recommendations for select patients (eg unstressed dogs), treatment decisions are then actually largely based on clinical assessment, suggesting the uncertainty of this monitoring method.

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Braddock JA, Church DB, Robertson ID, Watson AD. Trilostane treatment in dogs with pituitary-dependent hyperadrenocorticism. Aust Vet J 2003; 81:600-607

Bonadio CM, Feldman EC, Cohen TA, Kass PH. Comparison of adrenocorticotropic hormone stimulation test results started 2 versus 4 hours after trilostane administration in dogs with naturally occurring hyeradrenocorticism. J Vet Intern Med 2014; 28:1238-1243

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test in dogs. MS thesis, Faculty of Veterinary Science, University of Sydney, Sydney, Australia, 1998

Foster SF. Questions Trilostane Study. J Am Vet Med Assoc 2011; 239:1048

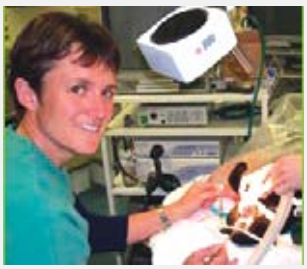
Griebsch C, Lehnert C, Williams GJ et al. Effect of trilostane on hormone and serum electrolyte concentrations in dogs with pituitary-dependent hyperadrenocorticism. J Vet Intern Med 2014;28:160-165

Graham P. Can we trust the numbers? Daunting Lessons from the ESVE Laboratory Quality Assurance Scheme. Proceedings: ECVIM Conference Malta, 2017

Macfarlane L, Parkin T, Ramsey I. Pre-trilostane and three-hour post-trilostane cortisol to monitor trilostane therapy in dogs. Vet Rec 2016; 179:597-

Sieber-Ruckstuhl N. Agreement of two pre pill cortisol measurements in dogs with hypercortisolism treated with trilostane. Abstract. ECVIM Conference, Malta September 2017.

1. See https://www.facebook.com/theESVE/posts/project-alive-2017-agreeing-language-in-veterinary-endocrinology-has-entered-the/887032924806681/ Accessed 23rd August 2018
2. See: https://www.dechra.co.uk/therapy-areas/companion-animal/endocrinology/canine-hyperadrenocorticism/vetoryl-monitoring-1?utm_source=directmailing&utm_medium=link&utm_campaign=PreVetorylCortisolSuperPage. Accessed 23rd August 2018



Dr Sue Foster (Vetnostics Medical Consultant) is available to discuss canine and feline medical cases.

Sue can be contacted via **1300 838 765.**

If leaving a voicemail message, please also leave the relevant Vetnostics laboratory number so that Sue can review the results before returning your call.