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Evidence-based approaches to reducing in-patient stress – Part 2: Synthetic pheromone preparations

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ABSTRACT: This article is the second of three that examine why hospitalisation is stressful, and why and how to reduce that stress. In it, I review the evidence for using synthetic pheromone preparations to relieve in-patient stress. I conclude that there is no robust, published evidence to support such use, and that environmental enrichment is a more logical approach.

The principle of keeping confined animals humanely is to provide them with some control over their environment and the facilities to perform highly motivated behaviours (Young, 2003). Most zoos, animal shelters and laboratories have made provision of such housing a priority. Provision of such housing is also implied in the Animal Welfare Act (2006).

Veterinary practices, however, have not typically provided it. Instead, they often use synthetic pheromone diffusers or sprays (Feliway and Adaptil [formerly DAP], Ceva Animal Health) to relieve in-patient stress.

However, in my opinion, a critical review of the literature indicates that there is little or no robust evidence that these preparations have been shown to be effective in veterinary hospital wards.

That does not mean that in-patients suffer as a result. As noted in the first paper in this series, stress is not a bad thing unless it is prolonged and the animal cannot adapt to it. Many can, some cannot.

Meanwhile, stress-related behaviours can make it harder to care for in-patients. So, it is important for animals and clinical personnel that, if a practice is relying on pheromone preparations, they should be effective.

This article now examines the evidence, starting with what pheromones are and how animals detect them. (NOTE: a critical review of the research on and use of pheromone applications in the *domestic* setting is outside the scope of this paper.)

What are pheromones?

Pheromones are chemicals that are individual to each animal and provide a form of communication with other individuals, usually of the same species.

How do pheromones work?

Pheromones are released from the body into the environment – for example, when cats scratch their claws against trees or furniture, or rub their faces against door-frames and other areas. When other individuals detect the pheromones, they undergo general changes in physiology and behaviour, such as showing increased interest (Mills, 2005).

How do animals detect pheromones?

The detection of pheromones is complex. Briefly, pheromone secretions contain the chemical's odour and the unique ancillary odours of the individual (Lindsay, 2000; Miklosi, 2007; Mills, 2005; Pageat & Gaultier, 2003).

The smell of the pheromones – which may first be signalled to other animals visually, by the presence of scratch marks, for instance – is detected in the normal way via the nasal chambers and olfactory bulbs. This stimulates the opening of the vomeronasal organ in the roof of the mouth and aspiration of the pheromone:

- in cats, aspiration is achieved through flehmen behaviour, with its characteristic retraction of the upper lip and partly opened mouth
- in dogs, aspiration is thought to be achieved by the dog's pushing his/her tongue against the roof of the mouth very rapidly. The dog's teeth sometimes chatter and you may see foam collecting on the upper lip.

The vomeronasal organ is innervated by three nerves, which provide links to the

limbic system – that part of the brain that regulates emotions, mood and memory. Animals who detect pheromones show activity in the limbic system and the hypothalamus, and changes in physiology and behaviour.

We shall now consider commercial pheromone preparations.

Feline facial pheromone

Feliway is a synthetic analogue of the F3 facial pheromone, which is one of five secreted by glands in the cat's chin, lips, vibrissae area and cheeks (Mills, 2005; Pageat & Gaultier, 2003). Cats deposit F3 on their surroundings when they rub their cheeks along them. They seem to prefer edges for this – a reason that boxes may be better than igloo beds for in-patients.

The F3 pheromone is thought to help the cat to identify those areas as being his or her territory. This is thought to reassure the cat about the area in which he or she finds his or herself. For this reason, pheromones are now recommended as part of International Cat Care's Cat Friendly Clinic Scheme, which is based on international guidelines (Roden et al., 2011).

Those guidelines state: 'Studies show that a synthetic FFP [feline facial pheromone] analog may have calming effects in stressful environments, reducing anxiety, fear and aggression, and increasing normal grooming and food intake in caged cats.' In support of this, Roden et al., (2011) cite two primary research papers concerning hospitalised cats, (Griffith, Steigerwald & Buffington, 2000; Kronen et al., 2006) and a critical review (Frank et al., 2010).

However, as noted by Frank et al. (2010), neither of those primary research papers offers clear evidence that synthetic FFP calms cats in the veterinary ward. This is because both papers demonstrate flaws in the study designs and are open to some *a priori* objections, as outlined below. The first paper (Griffith, Steigerwald & Buffington, 2000) describes two double-blind studies that examined the effect of Feliway spray in sick and healthy hospitalised cats. Both studies demonstrated methodological weaknesses (Griffith, Steigerwald & Buffington, 2000), including the following three points.

1. The cats were 'alternately assigned' to treatment or placebo groups. This was systematic allocation, not randomisation (Schultz & Grimes, 2002). Consequently, the apparent differences between the treatment groups cannot be definitively attributed to the treatments (Norman & Streiner, 2003).
2. The authors used several measures of treatment effect, which made it more likely that some measures would show a treatment effect owing to chance alone (Type 1 error) (Pocock, 1997; Senn & Bretz, 2007). That was not controlled for or discussed, which undermines their tentative conclusion that: 'Exposure to FFP [feline facial pheromone] may be useful to increase food intake of hospitalized cats.'
3. In the second study, there was no control group for Feliway. All cages were sprayed with the product; some had a cat carrier in the cage but the others did not. Food intake was increased significantly (three-fold) in the group with carriers.

The authors concluded that: 'Addition of the cat carrier to cages of the FFP-exposed cats resulted in a further significant increase in food intake.' However, that is erroneous because Feliway was not controlled for and using the previous study as a retrospective control was not valid.

The second citation by Roden et al. (2011) was by Kronen et al. (2006). They examined the effect of Feliway – when used with or without acepromazine – on 77 cats that had already been pre-medicated with analgesics. This study had a complex design, with appropriate randomisation, blinding, control and behavioural-measurement method.

The main outcome of interest was whether cats struggled during venous catheterisation. Feliway did not demonstrate a calming effect.

There were 12 other behavioural measures of efficacy, all recorded while the cats were still caged. The authors reported statistically significant effects on two of those measures (head position and position in the cage). However, this may have been another Type 1 error (Pocock, 1997; Senn & Bretz, 2007). Consequently, it was not clear from the reported statistics that Feliway reduced stress in the cats while they were caged.

The third citation by Roden et al. (2011) was an independent critical review of the previously discussed papers by Frank et al. (2010), who also concluded that the research provided 'insufficient evidence' of efficacy.

Dog-appeasing pheromone

Adaptil is a synthetic version of a pheromone present in sebaceous gland secretions from the intermammary sulcus. The pheromone serves to calm the suckling litter, and it is thought only to be present from three to four days after parturition to two to five days after weaning (Miklosi, 2007; Mills, 2005; Pageat & Gaultier, 2003). It is not clear why weaned dogs would retain the capacity to respond to – or even detect – that pheromone.

In the wild, the capacity would seem to have little adaptive value, but artificial selection may have enabled domestic breeds to retain the capacity to detect the pheromone and respond to it.

The mode of action of Adaptil is unclear but may be related to effects on prolactin, which can act as a neurotransmitter and may help reduce anxiety (Siracusa et al., 2010).

As with Feliway, there is little published research on the use of the product in the veterinary ward area.

One paper examined the use of Adaptil spray for managing pre-operative stress in 46 dogs taken to a veterinary teaching hospital for routine neutering (Siracusa et al., 2010). In general, the study had good design and analysis.

The authors noted statistically significant differences between Adaptil and placebo groups in both serum prolactin concentrations and in 'alertness and visual exploration behaviours after surgery'. However, the paper does not give the mean data for the groups, so it is not clear if the statistical differences were clinically significant.

Another study examined the effects of an Adaptil diffuser in 43 dogs over four days in a veterinary ward (Young-Mee et al., 2010). The authors reported 'overall amelioration of separation-related behavioral signs in the DAP-treated group'.

Again, the sample was not properly randomized (Schultz & Grimes, 2002) and the paper does not give sufficient

information to demonstrate whether the statistical method was applied correctly. As a result, it is unclear whether the reported improvement in the behaviours was clinically significant or a statistical artifact.

General points

In addition to the above difficulties, none of the papers satisfy the following doubts.

1. Pheromone secretions include the individual's unique protein marker/scent, which helps stimulate the vomeronasal organ to open. Understandably, it is impossible to supply those markers in the commercial products (Pageat & Gaultier, 2003). Instead, the products contain very high concentrations of the synthetic pheromones (Pageat & Gaultier, 2003).

   However, it remains unclear whether that is enough to consistently stimulate opening of the vomeronasal organ followed by the necessary aspiratory behaviour.

2. Aspiration into the vomeronasal organ requires flehmen in cats and 'tonguing' in dogs. These necessary behaviours may be difficult to detect, but careful video-recording should capture them in research studies. Nevertheless, the clinical trials of pheromones did not report measuring them (Griffith, Steigerwald & Buffington, 2000; Kronen et al., 2006; Siracusa et al., 2010; Young-Mee et al., 2010).

   a. Anecdotally, the behaviours are not apparent in wards where pheromone applications are used. This may be because no one sees the behaviours, especially if only one bout of aspiration into the vomeronasal organ is enough for stress-relieving effects, or that no one remarks on them.

   b. Another possibility is that the behaviours are not taking place at all. That seems more likely because of (i) the absence of the individual's unique odour molecules and/or (ii) the animal being more motivated to scan and cope with the unpredictable, uncontrollable hospital environment than to explore the cage for pheromones.

3. Diffusers would seem unlikely to provide adequate concentrations of pheromones within hospital cages.

The manufacturer notes for Feliway spray, in connection with urine spraying: 'Never use strong smelling disinfectants, bleach, biological washing powder, detergents or deodorisers to clean the affected areas. They may interfere with the action of Feliway and the strong smell may upset your cat further' (Ceva Animal Health, 2013).

This suggests that any impact of Feliway (and presumably Adaptil) sprays might be reduced where cages and bedding have been washed in biological detergent and/or bleach or other disinfectants. That could also explain the lack of evidence for efficacy in the published data.

Conclusion

In my opinion, the principal causes of in-patients' stress are the lack of environmental control and predictability. Pheromone applications alone cannot address this, so it is perhaps unsurprising that, while there may be widespread belief in the efficacy of these preparations in calming in-patients and anecdotal reports of such efficacy, the clinical trials published to date do not provide robust evidence to support efficacy.

In light of in-patients' needs for environmental control, it seems more logical for practices to ensure they provide ethologically relevant housing – with environmental enrichment, for instance.

That is the primary focus of the guidelines for the Cat Friendly Clinic Scheme (Roden et al., 2011) and it follows the trend in human hospitals (British Medical Association, 2011). It is also the standard of animal shelters, zoos and laboratories (Young, 2003).

The next article will outline relevant research on environmental enrichment and suggest some ways to provide it in veterinary wards. VN

References

ANIMAL WELFARE ACT. (2006) [Online] Available from: http://www.legislation.gov.uk/ukpga/2006/45/contents [Accessed: 13th Jan 2014].

BRITISH MEDICAL ASSOCIATION.(2011). [Online] *The Psychological And Social Needs Of Patients.* British Medical Association Science and Education. Available from: http://bmaopac.hosted.exlibrisgroup.com/exlibris/aleph/a21_1/apache_media/G8KXL7EIUQNLK7RQTQ5EP9ERF4AF1L.pdf [Accessed: 13th Jan 2014].

Ceva Animal Health (2013) [Online] *Feliway 60ml Spray. Handy hint.* Available from: http://www.ceva.co.uk/Products/Products-list/Feliway-60ml-Spray [Accessed: 13th Jan 2014].

FRANK, D., BEAUCHAMP, G. & PALESTRINI, C. (2010.. Systematic Review Of The Use Of Pheromones For Treatment Of Undesirable Behavior In Cats And Dogs. *Journal of the American Veterinary Medical Association* **236**: 1308-1316.

GRIFFITH, C. A., STEIGERWALD, E. S. & BUFFINGTON, C. A. T. (2000). Effects Of A Synthetic Facial Pheromone On Behavior Of Cats. *Journal of the American Veterinary Medical Association* **217**: 1154-1156.

KRONEN, P.W., LUDDERS, J. W., ERB H. N., MOON, P. F., GLEED, R. D. & KOSKI, S. (2006). A Synthetic Fraction Of Feline Facial Pheromones Calms But Does Not Reduce Struggling In Cats Before Venous Catheterization. *Veterinary Anaesthesia and Analgesia*, **33**: 258-265.

LINDSAY, S. (2000) *Handbook of Applied Dog Behavior and Training: Volume 1. Adaptation and Learning.* Ames. Iowa State University Press.

MIKLOSI, A. (2007). *Dog Behaviour, Evolution, and Cognition.* Oxford. Oxford University Press.

MILLS, D. (2005). Pheromonatherapy: Theory And Applications. *In Practice* **27**: 368-373.

NORMAN, G. R. & STREINER, D. L. (2003). *PDQ Statistics.* 3rd ed. Hamilton. BC Decker Inc.

PAGEAT, P. & GAULTIER, E. (2003). Current Research In Canine And Feline Pheromones. *The Veterinary Clinics Small Animal Practice* **33**: 187-211.

POCOCK, S. J. (1997). Clinical Trials With Multiple Outcomes: A Statistical Perspective On Their Design, Analysis, And Interpretation. *Controlled Clinical Trials*, **18**: 530-545.

RODEN, I., SUNDAHL , E., CARNEY H., GAGNON A-.C., HEATH, S., LANDSBERG, G., SEKSEL, K. & YIN, S. (2011). AAFP And ISFM Feline-Friendly Handling Guidelines. *Journal of Feline Medicine and Surgery* **13**: 364-375.

SCHULZ, K. F. & GRIMES, D. A. (2002). Generation Of Allocation Sequences In Randomised Trials: Chance, Not Choice. *Lancet* **359**: 515-519.

SENN, S. & BRETZ, F. (2007). Power And Sample Size When Multiple Endpoints Are Considered. *Pharmaceutical Statistics* **6**: 161-170.

SIRACUSA, C., MANTECA, X., CUENCA, R., ALCALÁ, M. DEL, M., ALBA, A., LAVÍN, S. & PASTOR, J. (2010). Effect Of A Synthetic Appeasing Pheromone On Behavioral, Neuroendocrine, Immune, And Acute-Phase Perioperative Stress Responses In Dogs. *Journal of the American Veterinary Medical Association* **237**: 673-681.

YOUNG, R. J. (2003). *Environmental Enrichment for Captive Animals.* Oxford. Blackwell.

YOUNG-MEE, K., JONG-KYUNG, L., ABD EL-ATY, A. M., HWANG, S.-H., LEE, J.-H. & LEE, S.-M. (2010). Efficacy Of Dog-Appeasing Pheromone (DAP) For Ameliorating Separation-Related Behavioral Signs In Hospitalized Dogs. *Canadian Veterinary Journal* **51**: 380-384.

Further reading

HEATH, S. (2011). Behavioural Considerations For Hospitalized Patients. 54th *Annual Congress of the British Small Animal Veterinary Association -Conference Proceedings* British Small Animal Veterinary Association. Quedgeley, pp116-118.

NORMAN, G. R. & STREINER, D. L. (2003). *PDQ Statistics.* 3rd ed. Hamilton. BC Decker Inc.

RODEN, I., SUNDAHL, E., CARNEY, H., GAGNON, A-.C., HEATH, S., LANDSBERG, G., SEKSEL, K. & YIN, S. (2011). AAFP And ISFM Feline-Friendly Handling Guidelines. *Journal of Feline Medicine and Surgery* **13**: 364-375.

YIN, S. (2009). *Low Stress Handling, Restraint and Behavioral Modification. Techniques for Developing Patients Who Love Their Visits.* San Francisco. CattleDog Publishing.