

A review of the effectiveness of clomipramine hydrochloride as an adjunct to behavioural therapy in the treatment of canine separation anxiety

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Introduction

Separation anxiety, defined as excessive vocalisation, inappropriate elimination and destructiveness associated with owner absence, is the second most frequently encountered behavioural disorder presenting to veterinarians (Takeuchi, Houpt and Scarlett 2000). The common sequelae of this are abandonment to shelters or euthanasia, whether due to owner ignorance of underlying causes, or inability to comply with behavioural modification techniques. Clearly, a simple, safe and exoteric treatment could improve the quality or save the lives of many dogs.

Discussion

In April 1998, Novartis Animal Health received European marketing approval for Clomicalm®, a serotonin re-uptake inhibitor (SSRI) containing clomipramine hydrochloride. Heralded an 'innovative medication offer(ing) veterinarians a fast-acting effective way of easing the symptoms of separation anxiety' (Görtler, Head of Novartis Animal Health, 1999), an early clinical trial (Simpson, 1997) supported this: dogs diagnosed with separation anxiety were significantly improved more frequently in dogs treated with clomipramine as an adjunct to behavioural modification, than those treated by behavioural modification alone. However, four years on, there is contradiction between recent clinical trials regarding the effectiveness of clomipramine in this situation, introducing the hypothesis that stand-alone behavioural modification programmes could be just as effective without this pharmaceutical intervention. The aim of this review is to revisit these trials and suggest reasons as to why contradictions exist.

In 1999, 2 clinical trials (Podberscek, Hsu and Serpell, 1999; Petit, Pageat, Chaurand, Heude, Beata and Dehasse, 1999) were separately conducted to evaluate the effectiveness of clomipramine in the treatment of separation anxiety in dogs. Both studies were essentially similar in design. Dogs previously diagnosed as having separation anxiety were chosen and randomly assigned into treatment groups that consisted of either a placebo or clomipramine administered at one of several dosage rates. In both studies all dogs received behavioural therapy during the trial regardless of the group assigned. The results were analysed using various statistical methods that determined differences between the treatment groups. This analysis was based on questionnaires completed by owners, which involved rating the dog's behaviour against a 5-point scale on both the initial consultation and at regular intervals during the trial. These intervals were different for the two studies, but both studies ran for approximately 2 months. The results of the two studies differed markedly. Podberscek et al (1999) found no evidence that clomipramine was any more effective than the placebo as an adjunct to behavioural therapy and maintained that the behavioural changes that clomipramine conferred could be attributed to its sedative effect. This result differs both from that of Simpson (1997) and of Petit et al (1999). The latter found their results clearly demonstrated clomipramine (at 1.0-2.0mg/kg b.i.d.) was a more effective adjunct to treating separation anxiety than a stand-alone behavioural modification programme. However, Podberscek et al (1999) admitted there were potential limitations to their trial and suggested larger, more closely matched treatment groups might go some way to eliminating these.

In 2000, CLOCSA study group published the results of a multi-centre clinical trial of similar design to Podberscek et al's (1999), but used 95 dogs meeting the criteria for the diagnosis of separation anxiety almost twice the number used in the earlier trial (49 dogs). CLOCSA study group's results provided evidence that clomipramine was an effective adjunct to a behavioural modification programme at the standard dose, causing improvement in signs

such as destructiveness and elimination at least 3 times faster than the placebo and in vocalisation between 1.5 and 3 times faster.

With four independent trials all being of very similar design, are there any intrinsic differences between Podberscek et al's (1999) trial compared to the others that could explain such differing conclusions?

The first striking difference between the trials is the number of dogs used as the study population. Aside from Podberscek et al (1999), in no other study considered here does the population consist of <70 dogs and Podberscek does comment on this as a potential limitation. They also comment that, despite Simpson (1997) using 77 dogs, the methods employed to estimate behavioural improvement were more subjective in nature than their own. Likewise, this could be said of the assessment methods used in the other studies, although all researchers attempted to reduce the degree of subjective bias. It is still possible, however, that owners reported non-existent changes due to some degree of placebo effect and that there were inconsistencies in owner toleration and, thus, assessment of improvement. It could be deemed necessary to undertake further research using qualified, objective professionals to assess behavioural improvements although it is the owner who will ultimately act upon their opinions and it could therefore be argued that it is valid to tolerate some degree of owner subjectivity when assessing the effectiveness of behavioural modifications (Takeuchi et al, 2000).

A more subtle difference between the studies was the structure and content of the behaviour modification programmes. Whilst all trials included such instructions as immediate cessation of retrospective punishment and owner-only initiated physical contact, the number and complexity of instructions in Podberscek et al's (1999) study was far greater than in the others. This could be significant. Takeuchi et al (2000) attempted to assess the degree of owner compliance with discharge instructions. They reviewed 52 dogs that had been diagnosed with separation anxiety 6 or more months after the initial diagnosis and found that significantly fewer dogs of owners who received >5 discharge instructions improved, as compared to those owners who received fewer. Furthermore, a higher percentage of owners complied with easy instructions such as no retrospective punishment, but instructions such as crate training and desensitisation programmes seemed more difficult. It is possible, therefore, that the contradictory results found between Podberscek et al (1999) and the other studies are actually not reflecting the effectiveness of clomipramine but the differing complexities of, and degree of owner compliance to, the suggested behavioural modification programmes.

Conclusions

From the evidence put forward, there is little doubt the clomipramine seems to improve the symptoms of separation anxiety in conjunction with behavioural modification therapy. However, if it is to be believed that complexity of behavioural modification therapy is directly correlated to owner compliance, then it could be said that clomipramine is only effective when a behavioural modification programme is exoteric in nature - and behavioural advice given to owners of dogs should attempt to be as simple and workable as possible. Further research is needed to assess the degree of owner compliance to discharge instructions, as there is certainly no evidence to suggest clomipramine is effective without behavioural modification, and research into the effects that clomipramine alone has on symptoms of separation anxiety could be viewed unethical. However, how much any treatment into separation anxiety is aimed at a symptom rather than a cause is debatable. Maybe to a degree there is need to turn to human lifestyle and the incorporation of dogs into that for an answer as to why some dogs find being home alone so disturbing.

Bibliography

King, J.N., Simpson, B.S., Overall, K.L., Appleby, D., Pageat, P., Ross, C., Chaurand, J.P., Heath, S., Beata, C., Weiss, A.B., Muller, G., Paris, T., Bataille, B.G., Parker, J., Petit, S.,

Wren, J., The CLOCSA (Clomipramine in Canine Separation Anxiety) Study Group (2000) Treatment of separation anxiety in dogs with clomipramine: results from a prospective, randomised, double-blind, placebo-controlled, parallel-group, multicenter clinical trial. *Applied Animal Behaviour Science* 67, 255-275

Petit, S., Pageat, P., Chaurand, J.-P., Heude, B., Beata, C. and Dehasse, J. (1999) Efficacy of clomipramine in the treatment of separation anxiety in dogs: clinical trial. *Revue Médicine Vétérinaire* 150, 2, 133-140

Podberscek, A.L., Hsu, Y. and Serpell, J.A. (1999) Evaluation of clomipramine as an adjunct to behavioural therapy in the treatment of separation-related problems in dogs. *Veterinary Record* 145, 365-369

Simpson, B. (1997) Treatment of separation-related anxiety in dogs with clomipramine. Results from a multicentre, blinded, placebo-controlled clinical trial. *Proceedings of the First International Conference on Veterinary Behavioural Medicine*. Eds D.S. Mills, S.E. Heath, L.J. Harrington. South Mimms, Universities Federation for Animal Welfare. pp. 143-154

Takeuchi, Y., Houpt, K.A. and Scarlett, J.M. (2000) Evaluation of treatments for separation anxiety in dogs. *Journal of American Veterinary Medicine Association* 217, 342-345

[http://www.info.novartis.com/media/press notes www/3166/clous-e.doc](http://www.info.novartis.com/media/press%20notes%20www/3166/clous-e.doc) -Hans-Beat Görtler, Head of Novartis Animal Health, Press Release, 6 January 1999