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Review Article

ORAL DRUG FORMULATION AND COMPLIANCE IN VETERINARY MEDICINE

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INTRODUCTION

Veterinarian perform a thorough examination, arrived at a correct diagnosis and recommended an appropriate treatment but poor compliance (Barter *et al.*, 1996) from the owners and/or pets to the advice given will potentially cause therapeutic failure. Long-term medication of tablets prescription to companion animals are particularly challenging especially in non-compliant pet (i.e. aggressive, fierce, fear biter). The successfulness of a long-term treatment is heavily dependent on owner compliance, their willingness and ability to administer the prescribed medication. Therefore, a suitable and user-friendly way of administrating drugs needs to be identified.

Veterinary compounding drugs

In general, tablets are allowed for administration of therapy without presence the veterinarians but owners' or companion animals' compliance can be a problem. Owners may fail to administer the tablet properly, their pets may not consume the entire tablet or only partial dose was administered especially in cats as this species at times can be difficult to medicate. To assist drug delivery and to encourage compliance, drugs are sometimes compounded by veterinarians, veterinary pharmacists or compounding pharmacists. To date, many studies and reviews of veterinary compound drugs have been published. They generally aim to; 1) to enhance consumer convenience and compliance; 2) to improve the pharmacokinetics of drugs and;3) to assure target and consumer safety (Ahmed and Kasraian, 2002; Merton Boothe, 2006; Papich, 2005). Drugs have been compounded for veterinary medical use because many were not in an ideal form of formulation to be used in the species being treated (cats, exotic animals and pet birds). To date, there are only a few approved veterinary formulations in the market(Hardee and Baggot, 1998).

An extemporaneously prepared compounding drug alters the original drug dosage formulation for ease of administration. Normally, conventional tablets will be crushed, capsules reformulated and solution altered to make it more convenient and palatable oral dosage formulation. Palatability, ways of administration, methods of dispensing and frequency of administration are factors that must be considered carefully when formulating a compounded oral drug for companion animals. The combination of these factors and the oral drug formulations produced must have good end result with regards to drug stability, purity and potency comparable to the original formulation (Hardee and Baggot, 1998; Papich, 2005).

The need of alternative formulations of drugs in veterinary medicine as well as in medical care for humans, particularly for use in paediatric patients, has lead to a boost of studies being conducted. Researchers have look into physiology function of the gastrointestinal tract of companion animals with drug performance (Sutton, 2004), comparison between different formulations in terms of drugs and products (e.g. in different packaging) stability assessment (Garner *et al.*, 1994), photosensitivity studies (Andrisano *et al.*, 1999), enantioselectivebehaviour and stereospecific of drug studies (Landoni *et al.*, 1997; Mehvar and Brocks, 2001). There are also published surveys and feedbacks on compliance with medication prescribed (Barter *et al.*, 1996), palatability studies (Hames *et al.*, 2008; Litster *et al.*, 2007) and preference of formulation (Cohen *et al.*, 2009). However, many have given great emphasized on the pharmacokinetics, pharmacodynamic and bioavailability of drugs (Arguedas *et al.*, 2008; Beddies *et al.*, 2008; Buck *et al.*, 1989; Flammer *et al.*, 2008; Jug *et al.*, 2009), all with the ultimate goal of producing a safe and suitable compounded oral drug formulation.

Oral formulation

Oral dosage consist of a large proportion of drugs formulations. Commonly, oral dosages are prepared in the form of solution, emulsion, suspension, gel/paste, powder, capsules and tablets. The solution, emulsion and suspension are generally in the form of liquid administered orally with an aid of a syringe. Where else, the gel and paste are semisolid precise oral dosage application on the upper gum or palate commonly supplied in pre-loaded calibrated syringes. The rate of paste drugs absorption would be expected slower than from a liquid but faster than the solid dosage form. Capsule is an easily digested and tasteless unit dose containers which allow accurate amount of drugs to be contain within a capsule. Different oral drug formulations such as powders, granules, pellets, suspension, emulsion or oils measured could capsulated but commonly intended for human usage and often contain an inappropriate dose for most animal species. Oral powder formulations are put on food during feeding time and must be palatable (Hardee and Baggot, 1998).

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However, conventional tablets are the most widely used oral drug administration in small animals. It has certain advantages over oral liquid dosage form. A tablet contains an equivalent dose of active drug in a compact form, easier to administer and usually presents the fewest problems with regard to stability. Bioavailability of a drug can vary widely among tablets because of the wide range of body weight, the total dose requirements of different species, the strength of the tablet (amount of the drug contained therein) largely determines its suitability for use in a particular species. Therefore, tablets are sometimes cut to avoid overdosing and this may lead to inaccuracy of medication if tables were not divided properly (Hardee and Baggot, 1998).

On top of that, tablet administrations are very challenging in non-compliant pets i.e. cats as they are notorious for ejection of tablets within second of their administration. In this circumstances, formulations such as liquid and paste may be better alternative or adding powder and granules into the food may be more convenient in non-compliant cats (Hardee and Baggot, 1998). Therefore, the pharmacodynamic, pharmacokinetics and bioavailability of different formulations of the same drug should be conducted and correlated to owners' and cats' compliance. It is crucial to determine which formulation would be cats' and owners' preference, good compliance practiced and achieved a good therapeutic effect. This applied the same for other species of companion animals too.

A few veterinary pharmaceutical companies have commercially produced drugs in other formulation and many veterinarians have compounded drugs in improve their therapeutic effectiveness. Veterinarians have assumed commonly that compounded oral formulations perform as well as the original formulation. However, this assumption should be investigated. Improper prescription of ineffectively compounded oral drug formulation would waste pet owners' time and potentially put at risk the health of the companion animal. Besides that, there is also a lack of studies on pet owners and companion animal compliance with regards to the usage of compounded oral formulation. More studies could provide useful feedback for pharmaceutical companies. This could lead to more compounded oral formulations of different drugs to be marketed and there could be a change in trends in oral drug formulation used by veterinarians.

Drug compliance

Drug compliance is generally described as the adherence of patients to their prescribed medication in human medicine (Besch, 1995; Cramer and Spilker, 1991; Haynes *et al.*, 1979). Therefore, drug compliance in veterinary medicine can be defined as the extent to which owners adhere to instruction when giving prescribed drugs to their animals. To date, veterinary drug compliance in veterinary medicine has been reported to range from 44% to 55% and human medicine has a wider percentage in comparison at 5% to 96% (Berendsen and Knol, 2002; Cramer and Spilker, 1991). The range of compliance supports the speculation in human medicine that patients do not adhere strictly to instructions for the use of medication. Poor compliance with drug therapy is widespread in all aspects of human medicine due to many factors (Cramer and Spilker, 1991; Haynes *et al.*, 1979; Mackner and Crandall, 2005). As animals are dependent upon their owner for administration of medication, there is every reason to assume that non-compliance is prevalent in veterinary medicine.

Therefore, alternative compounded drugs produced which have comparable or superior pharmacokinetic or pharmacodynamic to its original form should be investigated. The new alternative compounded formulation that may probably be not user friendly would defeat the purpose of effective therapeutic treatment and aid in compliance.

How to assess levels of compliance in veterinary medicine

Drug compliance has been measured and methods have been compared in several ways to assess levels of compliance directly (e.g. measurements of drugs in blood and urine excretion, measurements of biological or inert markers) or indirectly (e.g. therapeutic outcomes, clinical opinions, interviews, filling of prescriptions, pill counts, microelectronic monitors) (Besch, 1995; Cramer and Spilker, 1991; Haynes *et al.*, 1979). There is no one valid, reliable or novel method to assess drug compliance levels in veterinary and human medicine (Andersen *et al.*, 1995; Barter *et al.*, 1996; Cramer *et al.*, 1989; D'Souza *et al.*, 1983; Paes *et al.*, 1998; Partridge *et al.*, 2001; Udelson *et al.*, 2009). Most of the studies on drug compliance in veterinary medicine are based on short courses of medication in dogs (Barter *et al.*, 1996; Bomzon, 1978; Grave and Tanem, 1999) and no one has looked at drug compliance of cats and pet owners.

Pill counts were the simplest and cheapest method adopted but results obtained could be an over- and underestimation of compliance level as pet owners could give more pills than required or dispose of them (Bomzon, 1978; Grave and Tanem, 1999). Electronic monitoring involves placing a microchip on the container lid which records the number of times the lid was opened in a day. This method is expensive and could arouse suspicions as the containers looks different from normal dispensing containers. Pet owners might remove more than one dose or no dose while opening the lid which would reflect over- or under dosing (Barter *et al.*, 1996). Compliance in dosing intervals can be determined from the electronic monitoring which provides objective compliance measurements of daily dosing pattern and interval. This assessment is crucial as over-, under and erratic dosing intervals can diminish drug actions or cause adverse effects (Barter *et al.*, 1996). Therapeutic outcomes and monitoring with drug assays

using analytical techniques can be used to measured levels of compliance but such assays are expensive and subjected to individual pharmacokinetic variability. Veterinarians' assessment of client compliance (predictability) has been used but the validity of such a subjective and indirect measurement is questionable as veterinarians can overestimate the level of client compliance (Barter *et al.*, 1996). Owner self reports, interviews and questionnaires are methods by which owners are ask directly or indirectly regarding their compliance. These are simple and inexpensive methods that can easily be conducted in a veterinary practice. These methods allow pet owners to express problems encountered during drug administration and their observations (Barter *et al.*, 1996; Bomzon, 1978; Grave and Tanem, 1999; Litster *et al.*, 2007).

Factors affecting compliance

There are other factors that affect compliance levels besides the role of pet owners as administrators. Ease of administration is an important consideration when a drug is formulated. Generally, cats and dogs are administered tablets by placing the tablet at the base of their tongues (far back) and gently "poke down" the medication. The pet's mouth is quickly closed, the head returned back to the normal position and the throat is massaged or animal is distracted till medication is swallowed. Often, this is easier said than done particularly in cats as this species is more independent and less accustomed to being restrained. Also, there is the owners' fear of being clawed or bitten (Thombre, 2004). Therefore, the compliance level tends to decrease when a particular formulation is not user-friendly. To assist therapeutic treatment, alternative formulations which are easy to administer such as oral administration (solutions, suspension, paste/gels, capsules, powder/granules) (Hardee and Baggot, 1998) and transdermal application (ointment, cream, liquid) (MacGregor *et al.*, 2008; Magnusson *et al.*, 2001) have been compounded to enable owners to independently administer.

Palatability of oral formulations has been found to increase compliance level. Studies published in human medicine found that palatability is an important factor in drug compliance for children where the acceptability and ease of medication is greatly affected by its taste (Cifaldi *et al.*, 2004; Cohen *et al.*, 2009; Hames *et al.*, 2008). The term "palatability" refers to the voluntary (free choice) acceptance of ingestion of a pharmaceutical composition by companion animals, which is measured by a standard palatability test; acceptance and preference testing (Litster *et al.*, 2007; Thombre, 2004). Palatability is a desired attribute because it affects convenience and compliance, especially if medication has to be administered as a lifelong therapy e.g. given every day. Palatable oral formulations produced by pharmaceutical companies are commonly achieved by masking the taste and odour of drugs using chemicals, additives and flavourings(Thombre, 2004).

Other strategies can be adopted to minimise non-compliance by pet owners such as the clarity of instructions of prescription. They should be written clearly and backed up verbally to educate pet owners regarding the methods and intervals of administration. Changing a treatment regime from three times a day to twice daily and choosing a more appropriate dose or formulation would enhance compliance and effective treatment. Compliance levels also increase if owners are given more information regarding the condition being treated and the treatment provided if the veterinarian has spent sufficient time with pet owners during consultation (veterinarian-client-pet relationship) (Berendsen and Knol, 2002; Chapman, 1996; Cramer and Spilker, 1991; Grave and Tanem, 1999).

CONCLUSION

Oral formulation is a reliable method of administration. Currently, tablets at times have been substitute by paste and suspension formulation in clinical practice in doses equivalent to those given as tablets. To our knowledge, many studies has published reporting about specific drug plasma concentration and the pharmacodynamic effects but not many has looked at other formulations in comparison to tablet. Surveys or questionnaires documented to quantify owner preference and compliance towards different formulation of a drugs during administration are limited in veterinary medicine.

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