Pharmacogenetics for pain

Does pharmacogenetics play a role in the management of pain in companion animal species?

Pharmacogenetics is the study of genetics as it relates to individual variation in the response to drugs. Alterations in the genes coding for drug receptors, drug transporters and drug metabolising enzymes may cause clinical manifestations such as: altered drug efficacy; duration of action; or drug-drug interactions.

Although pharmacogenetics and personalised medicine are well established in clinical human medicine, they remain an area of emerging interest and ongoing research in veterinary science. Currently there are few studies describing how genetic polymorphisms may affect the efficacy of analgesic drugs used in companion animal species; or conversely, the occurrence of adverse drug reactions. This article aims to review some of the recent literature describing pharmacogenetic differences in dogs and cats.

Drug metabolising enzymes
Cytochrome P450 isoenzymes (CYPs) are a superfamily of hepatic enzymes. They are involved in the metabolism of a wide range of endogenous (eg steroids and fatty acids) and xenobiotic compounds. CYP enzymes are divided into families identified by numbers; CYP1, 2 and 3 and subfamilies designated by capital letters (eg CYP2B). Individual members of a subfamily (ie represented by a single gene) are identified by a further number (CYP2B11). CYP enzymes are responsible for the metabolism of many anaesthetic and analgesic drugs.

CYP2B11 (human equivalent CYP2B6)
In dogs, the CYP2B11 enzyme metabolises several sedative and anaesthetic drugs in vitro, ie: medetomidine, midazolam, ketamine, propofol and atipamezole. Whilst midazolam and ketamine are substrates for this enzyme, medetomidine and atipamezole are inhibitors. Although breed-related differences in CYP enzyme expression have been described, detailed information about the activity of the enzymes is lacking. Previously, CYP2B11 was identified as the enzyme responsible for the metabolism of propofol in Greyhounds; genetic polymorphisms have not been reported in this breed but pharmacokinetic differences exist.

A preliminary study describing polymorphisms in the canine CYP2B11 gene identified breed-specific abnormalities in: Collies, Labrador Retrievers and German Shepherd Dogs. In an unrelated study, the Border Collie, Labrador Retriever and German Shepherd were found to exhibit genetic polymorphisms within the CYP1A2 and CYP2B11 genes. The authors assert that alterations in drug sensitivity may result from these genetic changes.

In dogs, methadone is reported to be a CYP substrate and may be metabolised primarily by CYP2B11, which contrasts with humans. It remains unclear whether genetic polymorphisms in this enzyme affect the efficacy of methadone in dogs.

CYP2D15 (human equivalent CYP2D6)
In dogs, tramadol has little reported analgesic efficacy. This is thought to result from its metabolism and rapid conjugation and elimination in the urine. In humans, CYP2D6 is responsible for the metabolism of tramadol to the active metabolite M1, which is attributed with the major analgesic effect of the drug. Thus far no studies have determined whether genetic polymorphisms could affect the efficacy of tramadol in the dog.

A study performed in Beagle dogs identified differences in the duration of action of the non-steroidal anti-inflammatory drug cimicoxib (Figure 1). Dogs were designated arbitrarily as: extensive metabolisers (EM) and poor metabolisers (PM) on the basis that differences in pharmacodynamic effects were attributable to alterations in CYP2D15 enzyme activity.