An Introduction to Veterinary Medicine

for pharmacists and suitably qualified persons

Edited by

STEVEN KAYNE BSc, PhD, MBA, LLM, MSc (Med Sci), DipAgVetPharm, FRPharmS, FCPP, FIPharm FFHom MPS (NZ) FNZCP

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CONTRIBUTORS

Andrew Cairns BSc MPHarmS
Veterinary Pharmacist. Chairman of the Veterinary Pharmacists Group of the Royal Pharmaceutical Society. Dumfries, Scotland.

Graham Cawley MSc, MS, BVMS, MRCVS
Veterinary Surgeon, Cumbria, England.

Colin Chapman BPharm, BVSc(Hons), PhD, FPS (Australia)
Immediate Past Dean, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Professorial Fellow, Australian Health Workforce Institute, University of Melbourne, Science Fellow, Australian Pesticides and Veterinary Medicines Authority, Canberra, Australia.

Sarah Cockbill BPharm, BPharm PhD LLM MPharm DipAgVetPharm FRPharmS FCPP MIPharmM
Veterinary Pharmacist. Senior Research Associate, Welsh School of Pharmacy, University of Cardiff, Wales. Member of VPC 2001–2009.

Francis Hunter MRCVS, Vet FFHom
Veterinary Surgeon. Former Chair British Homeopathic Association and Member of Advisory Board on the Registration of Homeopathic Products. Pulborough, Sussex, England.

Michael H Jepson BPharm, MSc, PhD, FRPharmS, MCPP, MInstPkg, FIPharmM, DHMSA, MBIRA (Hon)
Veterinary Pharmacist, Visiting Fellow and Former Head of Pharmacy Practice, University of Aston, Birmingham, England. Former Director RPSGB Veterinary Pharmacy Diploma Course and Member VPC 1994–2001.

Steven B Kayne BSc, PhD, MBA, LLM, MSc (Med Sci), DipAgVetPharm, FRPharmS, FCPP, FIPharm FFHom MPS (NZ) FNZCP
Veterinary Pharmacist. Director RPS/HAUC Veterinary Pharmacy Education Programme. Member of VPC. Glasgow, Scotland.

David Keith BSc DipAgVetPharm MRPharmS
Veterinary Pharmacist, Bewcastle, Cumbria, England.

John Millward B.Sc (Hons), CBiol, MSB
Head of the Animal Medicines Inspectorate, Veterinary Medicines Directorate, Addlestone, Surrey, England.

Robert Morris BSc, MRPharmS, MBA, Dip AgVet Pharm, Dip Marketing
Veterinary Pharmacist with wide experience of the marketing of veterinary medicines. Northampton, England.

Martin Shakespeare BPharm, MRPharmS, DipAgVet, DipCP(DES), RNR
Veterinary Pharmacist. Royal Navy. Yorkshire, England.

Keith Siddorn BSc (Hons) JP
Farmer, Meadow Bank Farm, Broxton, Cheshire, England. Keith is the fourth generation of his family to run this traditional 200 acre mixed farm that produces 4,000 bacon pigs per year and has a large diverse herd of traditional Hereford cattle, a few laying hens and small flock of Hebridian sheep. Member of VPC.

Peter Southgate BVetMed, MSc, MRCVS
Veterinary Surgeon RCVS Specialist in fish health and production. Founder member and former President Fish Veterinary Society. Dumfries, Scotland. Member of VPC.

Bob Stevenson BVMS CertPM MRCVS
Veterinary Surgeon, Chairman, Animal Medicine Training and Regulatory Authority of (AMTRA) and Former Chair British Veterinary Association. Consultant to the British Pig Association and the Usk Veterinary Practice, Usk, Monmouthshire, Wales.

Lucy Whitfield MA, VetMB, DLAS, MRCVS
Veterinary Surgeon, Director of Named Veterinary Surgeon Services at the Royal Veterinary College, London, England.

Barrie Wilton
Adviser on the management and healthcare of pigeons. Pigeon fancier for over 50 years. Former Director, Petlife International Limited, Bury St Edmunds, England.

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VETERINARY MEDICINES

Steven Kayne and Sarah Cockbill

In this chapter the characteristics of veterinary medicinal products are discussed. The legal aspects of supply are covered in Chapter 5. There is also a section on veterinary medicines in Chapter 16.

Definition

The term Veterinary Medicinal Product (VMP) is defined in the European Directive 2004 and in the Veterinary Medicines Regulations (see Chapter 5) as being:

- any substance or combination of substances presented as having properties for treating or preventing disease in animals; or
- any substance or combination of substances that may be used in, or administered to, animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

History

Development of veterinary medicine

Throughout many of the great epochs of human history there has been human interaction with animals. Even in ancient civilisations, such as those of Egypt, Greece, and Rome, animals played major roles in religion, mythology, the military and agriculture. The Egyptian *Papyrus of Kahun* (1900 BCE) and ancient Indian Vedic literature in offer the first written records of veterinary medicine. Gradually animals came to be used for travel, food sources and advancements in scientific study. Increasing dependence on animals made it imperative that doctors be trained to care for their health and welfare. Evidence discovered in the primitive

societies of Mesopotamia and Egypt dates the beginning of the development of veterinary medicine to around 5000 years ago. The first evidence we have of the veterinary medical profession arises from ancient documents such as the Kahun Veterinary Papyrus, discovered in Egypt and dating around 1900 BC, the Hammurabis Code, arising from Babylonian society and containing codified prescriptions dealing with animals, and writings by famous philosophers such as Hippocrates and Aristotle. Generation after generation, there has continued to be development not only in the scientific and technological aspects of the field but also in the shaping of highly educated veterinarians interested in working to improve animal welfare. In ancient Mesopotamia the responsibility for protecting animals often fell under the jurisdiction of the priests, otherwise known as magi. Disease was seen as a sign of deity's displeasure, and the priests therefore intervened to appease the gods when faced with disease. There was encouragement for the development of specialists to be mediators between the gods and their human servants. Owners sought communion with the gods by asking priests to intervene in the hope of preserving the health of their ailing beasts. Due to their devout faith in animal gods, Egyptians developed prescriptions for animal protection. Ancient Greek and Roman societies began developments in veterinary medicine in similar, yet slightly different, directions than the Egyptians. The oldest relics of Greek veterinary medicine are seen in mythology. Varro, an early Greek philosopher, studied the numerous diseases of horses and gave evidence of primitive prognosis and treatment. He linked the causes of animal diseases to heat, cold, overworking, insufficient rest and food taken immediately after work. Treatments were remedial, often involving rubbing with cool water, dressing the animal in oil, feeding it or covering it. If the treatment did not work, the animal was often killed by piercing it in the head and allowing it to bleed to death. In Roman times *veterinaria de medica* was practised in a *veterinarium*.

Claude Bourgelat opened the first school of veterinary medicine in Lyons, on February 13, 1762. The school was founded by Louis XV and was designed mainly for the study of the diseases and treatments of livestock. The main focus of study was devoted to equine medicine due to the heavy dependence on horses by the military at that time. Studies were offered in anatomy, botany, zoology, pharmacy, therapy, surgery, legal veterinary studies, animal husbandry and animal care. The term 'veterinary surgeon' was so coined in 1796 by the British Army's Board of General Officers to distinguish them from human surgeons. Before this, animal doctors were known as 'farriers'. The literature records the story of an ox, labouring under 'hopeless constipation', to which was summoned an old farrier. A lively trout was taken from a stream and committed to the patient's gullet with a confident assurance that 'it would soon work its way through the impediment affording speedy relief'. Needless to say both trout and ox died.

The adjective 'veterinary' was popularised by the Frenchman Benôit Vial de St Bel whose plan for 'an institute to cultivate and teach veterinary medicine' developed into Britain's first veterinary school in London that began issuing diplomas to practise the veterinary art in 1794.

Development of veterinary medicines

Veterinary practice during the latter years of the 19th century and first three decades of the 20th century developed slowly; veterinarians rolled pills and folded powders from ingredients bought in bulk. Their armamentaria included turpentine, that acted as a universal stand-by, together with liquid paraffin and castor oil, common salt, soapy water enemas, iodine for wounds and carbolic acid for disinfection. A turning point was the arrival of prontocil, a sulphonamide used to treat blood poisoning, which was brought to the market by the German company IG Farber in 1935. Vaccines against several important diseases of farm livestock were available and by the end of the 1930s the sheep diseases braxy, lamb dysentery and louping ill were under control. Calcium borogluconate was also introduced at this time for the treatment of milk fever, a condition that had troubled farmers for decades.

The sulphonamides were first produced in 1932 and became available in veterinary medicine sometime later. Their effectiveness against bacterial disease led to significant improvements in animal welfare. Because of their efficacy and relative cheapness sulphonamides are still widely used today. The sulphonamides were followed by the introduction of penicillins.

A revolution in parasitic therapy occurred with the discovery of the benzimadazoles in the early 1960s the first being tiabendazole. Since then, structural changes in the core structure have improved efficacy and safety. This in turn has improved output for farmers and animal health.

The distribution of veterinary drugs

According to veterinary pharmacist Douglas Davidson of Blairgowrie, Scotland, the bulk of animal medicines were distributed in the 1920s and 1930s through local rural pharmacies or sold nationally by pharmacy-connected companies, e.g. Hilstons, Day Son & Hewitt. Farmers diagnosed their animals' ailments and then bought the products over the counter (OTC) as necessary – of course there were no antibiotics to worry about at that time. Dips tended to be distributed by garages and hardware stores. Pharmacists had an important role in formulating dips, including arsenical sheep dips, compounding boluses and, certainly up to 1948, played a significant role in the practice of euthanasia where cats and kittens were unwanted or in cases were animals were seriously ill or suffering.

In the 1940s and '50s, when the expensive anthelmintics – phenothiazine and tiabendazole – came to the UK market, merchants became established by, in many cases, ex-staff from veterinary pharmacists' businesses. Following the National Health Service Act in 1948, pharmacists (even in rural areas) saw great opportunities from the new dispensing arrangements and neglected the veterinary scene. However, a few pharmacy specialist-oriented businesses, such as Jearys, Cox & Robinson, and R.D. Jones survived. With the introduction of the Veterinary Surgeons' Act, diagnosis and supply became the province of veterinarians.

VMPs may now be supplied by (see also Chapter 5):

- Veterinarians may prescribe and supply VMPs from all distribution categories.
- Pharmacists and Suitably Qualified Persons (who are qualified veterinary health advisers in the appropriate species' groups) are entitled to prescribe and/or supply products in the distribution categories POM-VPS, NFL-VPS and AVM-GSL from premises registered by the General Pharmaceutical Council and the VMD respectively (see Chapter 5).

SQPs are primarily employed by Merchants and Sadlers, but the 2008 Veterinary Medicines Regulations allowed them also to supply from registered pharmacies and, with effect from 1 April 2009, from premises in the RCVS Register of Veterinary Practice Premises. Qualified Veterinary Nurses can become SQPs providing they pass the examinations of an approved training body and join a register.

Market sector values (see also Chapter 9)

Statistics on the UK Veterinary Medicine Market are available at the NOAH website http://www.noah.co.uk In the 12 months to December 2009 the members of the National Office of Animal Health (NOAH) members accounted for £452 million of sales, representing around 90% of the UK animal health market (at ex-manufacturers prices, net of all discounts. The biggest market share is attributed to parasitacides and vaccines.

In 1986 around 70% of animal medicines were used in farm livestock. As Figure 3.1 shows, in 2009 companion-animal medicine sales exceeded food-producing animal medicine sales by value and this sector continues to grow.

Control of veterinary medicines and their use

The Veterinary Medicines Directorate (VMD) has primary responsibility for the authorisation scheme for veterinary medicines and their supply.

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VETERINARY VACCINES

Lucy Whitfield

History of vaccines

The term 'Vaccine' is derived from the latin word for cow, 'vacca', reflecting Edward Jenner's original attempt to prevent a more serious human disease, smallpox, by using a milder, related, cattle disease, cowpox.

As early as the 11th century, the Chinese noted that individuals who recovered from smallpox were immune to further infections and Practitioners deliberately transferred virus from an infected patient to a healthy patient by scarifying the skin in an attempt to protect them. Unfortunately, this is likely to have resulted in the deaths of as many patients as it saved before the practice of 'variolation' was later refined so that only milder cases were used as a source of virus and the survival rate in deliberately infected patients was improved.

At the end of the 18th century, the physician, Edward Jenner observed that milk-maids did not suffer from smallpox, while those around them did. Jenner observed that cows were affected by a similar skin disease, cowpox, which was also contracted by the milk-maids but which appeared to protect them from the related human virus, smallpox. Jenner proved his theory by deliberately infecting a boy with cowpox, then subsequently attempting to infect him with smallpox virus. This provided a much safer alternative to the 'variolation' technique using the actual human pathogen.

Vaccination was further developed by Louis Pasteur in the 1870's, when he showed that injection of old cultures (possibly containing dead bacteria) of 'fowl cholera' into chickens protected them against later exposure to live virulent cultures of the organism.

Currently, there are several hundred vaccines licensed for veterinary use in the EU and over 2000 licensed in the USA. Vaccines have been produced against viruses, bacteria and parasites.

Why use vaccines?

Vaccines are used in the control of human and animal diseases, following the old adage that "prevention is better than cure". Why is it important to prevent disease?

Any disease that causes illness in an animal will compromise its welfare. "Freedom from pain, injury or disease" is one of the Five Freedoms set out by the Farm Animal Welfare Council and used as a measure of an animal's well-being. Control and eradication of major infectious diseases has led to great improvements in animal health and welfare.

Infectious diseases may also cause economic loss, in terms of death of the animal (especially the more susceptible young or old individuals in the group), through the loss of production during the acute illness, or due to sequelae of disease that last for the animal's lifetime.

Vaccines may be used in a programme to eradicate disease from a population of animals. In immunising and protecting the susceptible population, the disease organism is no longer able to spread through and remain amongst that species, so may die out after a period of time. The ease of achieving this depends on the characteristics of the infectious organism and the effectiveness of the vaccine and the vaccination programme.

Vaccination of animals also contributes towards human health, in preventing animal-to-human transmission of disease, from either domestic or wild animals. Increasing consumer pressure against the use of therapeutics, such as antibiotics, to treat disease has encouraged research into vaccination to prevent disease rather than clinical or prophylactic treatment. However, some 'organic' systems also restrict the use of vaccines, which can reduce the options for disease prevention.

The immune system

The immune system allows an individual to combat the large variety of infectious agents that exist in the environment. The immune system can be divided by function into the innate system and the adaptive system. The innate system consists of physical and biochemical defences against invading organisms, such as the intact skin, lysozyme (in secretions such as tears), complement and phagocytic white blood cells, which engulf and destroy foreign particles.

Complement is a cascade series of enzymes that are triggered by micro-organisms; it binds to the cell membrane of the pathogen and causes cell lysis. The complement system also attracts phagocytic white blood cells to the site and contributes to the local inflammatory response.

Some invading organisms have developed methods of evading destruction by the phagocytic cells, or fail to activate the complement system. The body's phagocytic cells have non-specific receptors that allow them to attach to and engulf foreign organisms but some organisms can evade this 'recognition' system. The adaptive immune system has evolved to work in combination with the innate system to identify and present invading organisms for destruction.

The adaptive immune system counteracts invading organisms by producing a specific molecule (antibody) to attach to their surface, which activates the complement cascade and phagocytes. These antibodies, produced by the B lymphocytes of the adaptive immune system, act to 'visualise' infectious agents, marking them for attachment by phagocytes. Phagocytes have receptors for the 'constant end' of the antibody molecule, so will recognise antibody-coated, or opsonised, micro-organisms more readily, leading to rapid phagocytosis and destruction.

Antibodies

Antibodies are a group of specialised proteins that exist in the blood and tissue fluids of mammals. Each antibody is specific for and can bind to a particular infectious organism; the body is able to make millions of varieties of antibodies to attach to the huge number of possible invading organisms. Some organisms such as bacteria may be very large, so the antibody may bind to particular place or "antigen" on the cell surface.

The antibody molecule has two functional regions: the 'variable end' binds to the antigen and the 'constant end' to host tissues, such as phagocytic cells. Antibodies, or immunoglobulins, can be grouped into one of several classes, which have slightly different structures and may be predominantly associated with different regions of the body. IgG is the most abundant class of antibody and is the major circulating immunoglobulin. IgA is secreted from the epithelium of the intestinal and upper respiratory tracts and occurs in secretions such as milk and tears. It is involved in defences at the external body surfaces. IgE is important in some parasitic infections and in allergy.

Each antibody is produced by a particular line of white blood cells (B lymphocytes) each of which is programmed to make only one antibody, according to the specific receptor placed on its cell surface. When a particular antigen binds to the receptor, the cell is triggered to multiply and mature into both antibody-producing cells and memory cells. This is clonal expansion (Figure 4.1).

During the process, some of the cells mature into 'memory' cells. This allows the subsequent immune reaction to be much faster and larger, usually enabling the eradication of the organism before disease results.

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EQUINE HEALTH AND NUTRITION

Michael H Jepson

It is estimated that there are over 850,000 horses and ponies in the UK at the present time, most of which are kept for riding. Figures from the relevant Ministries in England, Scotland and Wales only give information about horses and ponies grazed on agricultural land, with no indication of the numbers of equines being kept on domestic premises, and therefore do not give an accurate picture of the equine population. The only subdivision on the census form is between animals owned and not owned by the occupier of the agricultural holding.

Figure 15.1 It is estimated that there are over 850,000 horses and ponies in the UK.

There are approximately 2,000 horses in the Greater London area – police horses, dray horses, animals belonging to riding establishments, and so on.

Horses and ponies, together with donkeys, are the most common species of the genus *Equus* that are kept domestically. The transition from being a major contributor to commercial haulage in the past to their present predominant role for riding for pleasure has resulted in equines being often considered today as 'companion animals' or even pets. However, it is worthy of note that, for some years and currently, there is considerable interest in reviving the use of heavy-breed draught horses in the UK, though this has been largely limited to show competitions and use by some breweries for promotional purposes and for local deliveries in a traditional way.

It needs to be recorded that in some EU member states horse meat is still used for human consumption, that horses are raised and exported as food-producing animals. Where this is the case, the restrictions that apply to the use of certain drugs or maximum residue limits will apply, and will be referred to later in this chapter. Broadly speaking, this is not an issue in the UK, and it is potentially relevant for any community pharmacist or merchant to consider whether there is a place for those animal medicines that can contribute to equine health. Medication for routine treatment of conditions that do not require diagnosis by a veterinarian, such as infection with gastrointestinal tract worms, can be appropriately supplied together with general advice about the choice of drugs available, frequency of treatment and the way in which, for example, the potential for resistance may be minimised by changing the chemical nature of the active ingredient used. A large proportion of horses and ponies are kept at livery stables and riding schools. Shared grazing is the norm, so it is imperative to worm horses regularly in order to maintain good health.

In the UK, Ireland and some other countries, horses may also be bred for specialist performance and leisure activities and are completely disassociated from human consumption. EU legislation requires that horses intended for breeding and production are accompanied by a passport, confirming whether or not the horse is intended for human consumption and, importantly, the passport includes a section that records all medicines administered to the animal. This legislation is important to the veterinarian in particular, as it enables the use of medicines, on appropriate occasions, that do not have an established maximum residue level.

Nutrition

Horses are herbivores, though their digestive system appears less specialised than that of the ruminant (see Chapter 17). The equine stomach is simple but the intestine is considerably modified, with an enlarged colon, in order to digest the

large quantities of roughage required. Microbial synthesis in ruminants and in horses makes these animals unlikely to experience thiamine deficiency. However, symptoms have been reported in horses that have consumed quantities of bracken (*Pteridium aquiline*), which contains thiaminase, a thiamine antagonist. The horse grazes one or two mouthfuls at a time by using its very strong and mobile lips to draw grass between its pairs of incisor teeth. The grass is ground briefly between the molars and swallowed. Horses avoid grass soiled by their faeces. Domesticated horses are routinely fed concentrates, but this may cause a problem if they contain too much grain. While the horse's teeth are suitably modified to crush grass into small pieces, they seem less able to crush grain efficiently. Food boluses normally pass quite rapidly through the stomach into the intestine, but if too much uncrushed grain is present this may swell in the stomach, causing distension and pain or colic.

Management

Awareness and understanding of equine management has greatly increased in recent years, and many former losses due to disease and injury are now avoided. The two major rules of management are to avoid overcrowding and to establish and maintain cleanliness. These fundamental needs, with so many parallels in health terms elsewhere, apply irrespective of the number of horses or of the size of the establishment. Unfortunately, pressures that favour economics often result in unsatisfactory compromise. It is important for all those concerned to recognise that the prevention of disease and injury is optimised by good nutritional management, housing and hygiene, vaccination programmes and internal and external parasite control. It is poor practice to rely on veterinarian service only when an acute situation presents. The prophylactic control of many conditions and diseases should be the rule, and this is where pharmacists and SQPs have a role to play alongside veterinarians. Animal health and welfare require team cooperation with the animal owner.

It should be emphasised that product literature for medicinal products with marketing authorisation for use in animals will give precise details about the animal species and indication(s) to which the licence applies. It is illegal, for other than a veterinarian under the 'cascade' arrangement, to direct the use of a product outside the licence (see Chapter 3). Certain cough remedies have frequently been purchased by horse owners for administration to their animals. Pharmacists should be alert to this situation, which on occasion may raise issues of short-term animal welfare, but such products are invariably licensed only for human use and may legally be supplied only on the authorisation of a veterinarian if intended for animal use.