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Veterinary pharmacovigilance. Part 3. Adverse effects of veterinary medicinal products in animals and on the environment

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Like humans, animals may experience adverse effects when treated with medicinal products. These effects may be related to the pharmacological or toxicological properties of the substances used or they may arise because of hypersensitivity. Veterinary medicinal products may also possess the ability to harm the environment. This paper reviews the potential of veterinary medicinal products to cause adverse effects in animals and on the environment.

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INTRODUCTION

Animals, like humans, are susceptible to the side-effects of medicines. Indeed, some species may be particularly sensitive to the toxic effects of some specific drugs (and other chemicals). For example, the cat has a very low capacity to conjugate paracetamol (acetaminophen) because of its low glucuronyl transferase activity. Hence, cats are extremely sensitive to the toxic effects of paracetamol, and what is a therapeutic dose in other species may prove to be a lethal dose in the cat (Campbell & Chapman, 2000a). Cats are also more susceptible to the toxic effects of permethrin because unlike some other mammalian species they lack the necessary detoxification pathways (Volmer *et al.*, 1998; Meyer, 1999; Gray, 2001; Martin & Campbell, 2000; Richardson, 2000). Dogs appear to be more sensitive to the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the gastro-intestinal tract, than do other species (Campbell & Chapman, 2000a).

SUSPECTED ADVERSE REACTIONS IN ANIMALS

Companion animals

Gastric effects are the major adverse drug reaction associated with nonsteroidal anti-inflammatory drugs. The major effect is gastric ulceration resulting from inhibition of prostaglandins and loss of cytoprotection (Bolte *et al.*, 1980; Stewart *et al.*, 1980; Van Ryzin & Trapold, 1980; Roudebush & Morse, 1981; Boulay *et al.*, 1986; Elliott *et al.*, 1988; Kore, 1990; Ohkubo *et al.*, 1990; Spellman, 1992; Vollmar, 1993; Knight *et al.*, 1996; Hawkey, 1999; Bertolini *et al.*, 2001; Boothe, 2001; Lee & Morris, 2001; Waller *et al.*, 2001; Ramesh *et al.*, 2002; Neiger, 2003; Tjälve, 2003). Some of these drugs may also cause disruption of thyroid function in dogs (Daminet & Ferguson, 2003). Two nonsteroidal inflammatory drugs, meclofenamic acid and phenylbutazone, have been associated with the induction of a plastic anaemia in dogs (Weiss & Klausner, 1990). Anaemia, thrombocytopenia and pancytopenia have also been reported in dogs following phenylbutazone treatments (Watson *et al.*, 1980). Pentosan polysulphate, which is not a member of this class of drugs but is used in the treatment of osteoarthritis in dogs, has a low order of toxicity and adverse effects are limited to lethargy and changes in demeanour (Hannon *et al.*, 2003).

Synthetic pyrethroids are extremely effective against fleas and other ectoparasiticides in the dog (Endris *et al.*, 2000, 2002, 2003) but because of their adverse effects in cats, they are usually contraindicated for this species (see Introduction). The newer ectoparasiticides for use on dogs and cats such as imidacloprid, fipronil and lufenuron have low toxicity (Stansfield, 1997; Hovda & Hooser, 2002), although there has been a report of adverse effects in a cat treated with imidacloprid. However, the animal also had a thymoma and was subsequently treated with other drugs (Godfrey, 1999). Fipronil may be toxic to very young rabbits, probably as a result of over dosing; it resulted in anorexia, lethargy and death (Webster, 1999).

Hypersensitivity effects have been widely reported in the literature (Yeary, 1975; Giger *et al.*, 1985; Ballarini, 1994; Noli *et al.*, 1995) along with diarrhoea and vomiting (Kunkle *et al.*, 1995). Diarrhoea, vomiting, loss of appetite and depression are common in dogs (and cats) with a variety of antimicrobial drugs (Kunkle *et al.*, 1995). Hypersensitivity reactions have been reported in dogs treated with oxytetracycline (Abdullahi & Adeyanju, 1985; Srinivasan *et al.*, 1991). Metronidazole may be toxic to dogs resulting in neurological signs and in severe cases, death (Wright & Tyler, 2003). Sulphonamides and potentiated sulphonamides have also been implicated in hepatic necrosis and

keratoconjunctivitis sicca in dogs (Morgan & Bachrach, 1982; Sutton & Roach, 1988; Gray, 1990; Bunch, 1993; Twedt *et al.*, 1997; Trepanier *et al.*, 2003). Streptomycin and dihydrostreptomycin may cause death in dogs after large intravenous doses, while the aminoglycoside antibiotics are ototoxic, and may be nephrotoxic in animals (Riskaer *et al.*, 1956; Yeary, 1975; Yakota *et al.*, 1984; Mealey & Boothe, 1994; Riviere & Spoo, 2001). Colitis may occur in dogs after antimicrobial treatments (Willard *et al.*, 1998). Blood dyscrasias have been reported in dogs following chloramphenicol treatment (Baig *et al.*, 2002). Epilepsy has occurred in dogs following large experimental doses of penicillin (Currie *et al.*, 1970), while amphotericin B may be nephrotoxic (Ndiritu & Enos, 1977; Ceylan *et al.*, 2003). Sulphonamide drugs may disrupt thyroid function in dogs when given at high doses (Daminet & Ferguson, 2003).

Toxic epidermal necrolysis (TEN), a serious condition occasionally seen in humans treated with drugs is occasionally seen in animals. TEN has been observed in dogs treated with antibiotics including gentamicin, cephalexin, chloramphenicol and potentiated sulphonamides (Roosje, 1991). Also rare it seems, is the possibility that companion animals may be pregnant when being treated (Landsbergen *et al.*, 2001), although many veterinary medicinal products carry warnings and contraindications for pregnancy, largely because they have not been tested for reproductive safety rather than due to any actual risk. Nevertheless, unfavourable reproductive outcomes do not feature in reports by the UK's VMD, and are rare in the open literature.

Calcipotriol and compounds related to vitamin D are toxic to dogs and may cause renal, splenic, gastric and myocardial mineralization (Campbell, 1997; Fan *et al.*, 1998; Durtnell, 1999; Hare *et al.*, 2000; Campbell & Chapman, 2000b; Torley *et al.*, 2002; Welch, 2002). Acepromazine may induce aggression in dogs (Waechter, 1982; Meyer, 1997).

Hepatotoxicity and cholestasis have been reported in dogs treated with phenytoin in combination with phenobarbital and primidone as anticonvulsant therapy (Bunch *et al.*, 1987). Similar effects have previously been reported in dogs treated with phenytoin (Nash *et al.*, 1977; Bunch *et al.*, 1982,1984; Bunch, 1993). Primidone has resulted in ataxia and collapse in the dog (Shield, 1987). The benzimidazole drug mebendazole and the anaesthetic methoxyfluorane have resulted in hepatic injury in the dog (Ndiritu & Weigel, 1977; Polzin *et al.*, 1981; Swanson & Breider, 1982).

Heartworm infection in dogs caused by *Dirofilaria immitis* tends not to be a problem in Northern Europe, but it can be a major parasitic condition in warmer areas. In the past this condition was treated with diethylcarbamazine and a severe adverse reaction, similar to hyovolaemic shock, was frequently reported (Sasaki *et al.*, 1986, 1989). This was accompanied by tissue damage, and particularly by hepatic injury (Powers *et al.*, 1980; Palumbo *et al.*, 1981; Desowitz *et al.*, 1984; Rawlings *et al.*, 1986). The mechanism is unknown but appears to be related to parasite burden; the reaction can be partly blocked by diazepam (Palumbo *et al.*, 1981; Desowitz *et al.*, 1984). The drug has now been largely displaced by more modern treatments for heartworm, including ivermectin and selamectin.

Saffan is an injectable veterinary anaesthetic for use in cats; it contains two steroidal anaesthetic agents, alfaxalone and alfadolone acetate. In humans (as Althesin) the product produces hypernoea on administration, and apnoea in overdose (Hunter, 1973). Oedema in the ears and paws has been reported in cats following its administration (Alcarez & Stone, 1980; Abou-Madi & Blais, 1987). Adverse effects in cats appear to be due to the release of histamine or histamine-like substances caused by a solubilizing agent Cremophor EL, a polyethoxylated castor oil derivative used in the formulation (Stogdale, 1978). Laryngeal oedema and pulmonary oedema have been reported (Stogdale, 1978; Harding, 1980). These may occasionally be severe and can result in death (Corbett, 1976; Stogdale, 1978; Dodman, 1980; McDonald, 1980) but adverse reactions to the product appear to be rare (Carroll, 1982). Saffan can also lead to marked depression of cardiopulmonary function in cats (Dyson *et al.*, 1987). There has been an isolated report of an anaphylactoid reaction to xylazine in the cat but most adverse events to this drug appear to be due to overdose which can be treated with tolazoline, doxapram or yohimbine (Arnbjerg, 1979; Jensen, 1985; van Metre, 1992; Raptopoulos *et al.*, 1993). Propofol has been reported to lead to convulsions in dogs (Helin *et al.*, 2001).

The antifungal drug griseofulvin has been shown to produce birth defects in laboratory animals. It produced teratogenic effects in rats when given oral doses of 250 mg/kg/day from days 6 to 15 after mating. No malformations were noted with 125 mg/kg/day (Klein & Beall, 1972). Similar results were noted in other studies in rats (Aujezdska *et al.*, 1978; Steelman & Kocsis, 1978). An *in vitro* study with rat embryos also suggested teratogenic potential (Bechter & Schmid, 1987).

Therapeutic treatment with griseofulvin of pregnant cats for ringworm resulted in malformations in the offspring including cleft palate, exencephaly, caudal displacement and hydrocephaly, along with multiple skeletal abnormalities including cranium bifidium, spina bifida and abnormal vertebrae. Cyclops and anophthalmia also occurred (Scott *et al.*, 1975). Similar cases in cats have been reported (Gillick & Bulmer, 1972; Gruffydd-Jones & Wright, 1977; Turner, 1977). Cats appear to be more susceptible to the toxic effects of griseofulvin (Kunkle & Meyer, 1987), but it is not known if this species is also more susceptible to the teratogenic effects of the drug.

Salinomycin has resulted in polyneuropathy in cats after oral intake through contaminated cat food (Van der Linde-Sipman *et al.*, 1999).

Interestingly, the predominance of adverse reactions in cats and dogs has been reported in other countries such as Australia and France (Keck & Lorgue, 1990; Maddison, 1992). There were other similarities too; for example, the occurrence of pyrethroid toxicity arising from the use of ectoparasiticides in cats and gastrointestinal effects resulting from the use of nonsteroidal anti-inflammatory agents in dogs (Maddison, 1992).

Although not indicated for use in hamsters, clindamycin and lincomycin have been shown to result in enterocolitis in this species (and in guinea-pigs) (Small, 1968; Lusk *et al.*, 1978; Onderdonk *et al.*, 1981). This is associated with one or more bacterial toxins, including clostridial toxins (Bartlett *et al.*, 1978;

Knoop, 1979; Toothaker & Elmer, 1984; Merrigan *et al.*, 2003). Lincomycin and clindamycin cause pseudomembranous colitis in humans (Scott *et al.*, 1973; Lee & Morris, 2001), and the hamster has been suggested as a model for the human disease (Price *et al.*, 1979).

Large animals

Many animals are specifically intolerant to the microbiological effects of some antimicrobial drugs (Keck & Ibrahim, 2001). For example, rabbits, hamsters, ruminants and horses rely significantly on the gut flora for digestion of plant material, particularly cellulose, and if the gut flora is inhibited or otherwise disrupted by some antibiotics, morbidity and death can occur (Killby & Silverman, 1967; DeSalva *et al.*, 1969; Milner, 1975; Olfert, 1981; Keen & Livingston, 1983; Gray, 1989, 1993; Rollin *et al.*, 1986). Adverse effects to antimicrobial drugs were reported relatively frequently in horses (Gray *et al.*, 2003). There was little description of these effects but gastrointestinal disturbances, including diarrhoea have been reported after treatment of horses with a number of antibiotics as has the development of *Clostridium difficile* colitis in mares following treatment of their offspring with erythromycin and rifampicin (Keen & Livingston, 1983; Wilson *et al.*, 1996; Baverud *et al.*, 1998; Stratton-Phelps *et al.*, 2000; Brumbaugh, 2001).

Ototoxicity and nephrotoxicity were observed in calves given neomycin (Crowell *et al.*, 1981), while cardiotoxicity and pulmonary oedema were noted in calves accidentally given a large overdose of doxycycline (Yeruham *et al.*, 2002). Pharyngeal and lingual paralysis have been reported in calves after doxycycline treatment (Chiers *et al.*, 2004). Procaine penicillin has resulted in toxicity in pigs. Animals became pyrexic and lethargic, with vomiting, inappetance and cyanosis of the extremities. Swelling of the vulva, mucous discharge and abortion occurred (Nurmio & Schulman, 1980; Embrechts, 1982). Hypersensitivity reactions and effects on the gastrointestinal tract have been described following tetracycline or penicillin treatment of cattle (Balasubramanyam, 1980; Sakar, 1993; Thirunavukkarasu *et al.*, 1995). Chloramphenicol has resulted in hypersensitivity reactions in large animals (Sudhan *et al.*, 1990; Bhat *et al.*, 1995).

Adverse effects, suggestive of anaphylaxis, have been reported in horses treated with penicillin, and signs of procaine toxicity, after treatment with procaine penicillin have also been noted (Eyre & Lewis, 1973; ap Rh. Owen, 1980; Farmer, 1980; Marshall, 1980; Xu & Liu, 1985; Allpress & Heathcote, 1986; Nielsen *et al.*, 1988; Chapman *et al.*, 1992; Kemble, 1995). In one report, of 11 horses treated with penicillin, 5 died. One had post-mortem findings suggestive of anaphylaxis, while in the others, the clinical signs suggested procaine toxicity (Nielsen *et al.*, 1988). Sudden death has been reported in a pony after treatment with a number of drugs including procaine penicillin and neomycin (McCann, 1995). There have been a number of cases of penicillin-induced immune-mediated haemolytic anaemia, one with hepatic failure, reported in horses (Blue *et al.*, 1987; Step *et al.*, 1991; McConnico *et al.*, 1992; Robbins *et al.*, 1993). Intravenous injection of trimethoprim-sulphonamide products has been associated with fatalities in the horse, while neomycin has resulted in nephrotoxicity (Alexander & Collett, 1975; Edwards *et al.*, 1989; Gray, 1989; Rohner & Demuth, 1994). Trimethoprim and sulphonamides has been reported to cause diarrhoea in horses, but its prevalence was similar to that noted following other antimicrobial drugs including penicillin (Wilson *et al.*, 1996). Erythromycin also causes diarrhoea in the horse (Stratton-Phelps *et al.*, 2000). On the other hand, the cephalosporin drug ceftiofur sodium appears to be relatively safe in the horse, at least after intramuscular administration (Mahrt, 1992).

Xylazine can occasionally result in extreme excitation in horses (Groenendyk & Hall, 1989).

Phenylbutazone is one of the most commonly used anti-inflammatory drugs in horses. It may induce gastric ulceration in the horse; there have also been reports of decreased bone mineralization in cortical bone following phenylbutazone administration, while eltenac resulted in dose-dependent NSAID toxicity; death may occur after doses in excess of those recommended (Jeffcott & Colles; 1977; Lees & Michell, 1979; Hamm *et al.*, 1997; Rohde *et al.*, 2000; Brumbaugh, 2001).

There are a number of reports on the induction of optic neuropathy and retinopathy in sheep and goats and other animals following treatments with the salicylanilide drug closantel (Button *et al.*, 1987; McEntee *et al.*, 1995; Gill *et al.*, 1999; Barlow *et al.*, 2002). This generally appears to follow over-dosing with the drug (Borges *et al.*, 1999). Overall, the drug has relatively low toxicity (Van Cauteren *et al.*, 1985). Levamisole is an anthelmintic drug used in animals which has also found a role in the treatment of cancer and rheumatoid arthritis in humans because of its immunomodulatory effects (Robens, 1984; Laurie *et al.*, 1989; Forman, 1994; Holcombe *et al.*, 1998; Moore & Haller, 1999; Yip *et al.*, 2000; Zlotta & Schulam, 2000). In humans, it may induce adverse effects including agranulocytosis and hypersensitivity reactions (Secher *et al.*, 1977, 1978; Mielants & Veys, 1978; Prieur *et al.*, 1978; Symoens *et al.*, 1978; Runge & Rynes, 1983). In animals, adverse effects are seemingly rare; the drug is well tolerated by a number of species, including birds (Buys & van der Made, 1977; Reinemeyer & Courtney, 2001). However, in the past, levamisole has been reported to be toxic in domestic animals and indeed, a report published in 1980 claimed that levamisole caused the greatest number of adverse effects reported to the FDA with pigs and cattle being the major species affected (Hsu, 1980). However, the use of levamisole is now much less widespread, often because of levamisole-resistant parasites and the alternative use and rotation of other anthelmintic drugs such as the benzimidazoles and the avermectins and related compounds. There have been reports of levamisole toxicity in treated animals (Babish *et al.*, 1990; Cawley *et al.*, 1993; Sarma & Sarma, 2002), and the drug may be more toxic when given with other medications such as diazinon (Ford & Abdelsalam, 1983; Abdelsalam & Ford, 1987).

The ionophore antibiotics such as lasolocid, maduramicin, monensin, narasin and salinomycin are widely used in poultry

for the prevention and treatment of coccidiosis caused by *Eimeria* species (Lindsay & Blagburn, 2001). They have narrow therapeutic indices, and are toxic to turkeys and mammals at relatively low doses (Todd *et al.*, 1984; Oehme & Rumbeiha, 1999; Lindsay & Blagburn, 2001). Ionphore toxicity, often with fatalities and frequently as a result of accidental treatment or misuse, has been reported in a number of species including rabbits, dogs, cats, pigeons, quail, chickens, turkeys, ostriches, goats, pigs, sheep, cattle, camels and horses (Matsuoka, 1976; Collins & McCrea, 1978; Malone, 1978; Donev *et al.*, 1980; Howell *et al.*, 1980; Wilson, 1980; Hanson *et al.*, 1981; Nuytten *et al.*, 1981; Halvorson *et al.*, 1982; Newsholme *et al.*, 1983; Van Vleet *et al.*, 1983; Wagner *et al.*, 1983; Anderson *et al.*, 1984; Todd *et al.*, 1984; Gad *et al.*, 1985; Reece *et al.*, 1985; Bourque *et al.*, 1986; Galitzer *et al.*, 1986; Potter *et al.*, 1986; Van Vleet & Ferrans, 1986; Egyed *et al.*, 1987; Rollinson *et al.*, 1987; Chalmers, 1988; Ficken *et al.*, 1989; Drumev *et al.*, 1990; Dalvi & Sawant, 1990; Groom & Beck, 1990; Kavanagh & Sparrow, 1990; Sawant *et al.*, 1990; Gregory *et al.*, 1992; Hazlett *et al.*, 1992; Mousa & Elsheikj, 1992; Novilla, 1992; Andreasen & Schleifer, 1995; Lehel *et al.*, 1995; Plumlee *et al.*, 1995; Bernáth *et al.*, 1996; Baird *et al.*, 1997; Hoop, 1998; Oehme & Pickrell, 1999; Roder & Stair, 1999; Van der Linde-Sipman *et al.*, 1999; Bila *et al.*, 2001; Jones, 2001; Agaoglu *et al.*, 2002; Condon & McKenzie, 2002). Cardiomyopathy, with dilated heart or petechial and ecchymotic haemorrhages have been noted in cattle poisoned with lasolocid and monensin (Potter *et al.*, 1984; Galitzer *et al.*, 1986; Mathieson *et al.*, 1990; Bastianello *et al.*, 1996; Basaraba *et al.*, 1999). Cardiomyopathy and myopathies have been seen in other species with ionophore poisoning (Wilson, 1980; Hanrahan *et al.*, 1981; Muylle *et al.*, 1981; Pressman & Fahim, 1983; Anderson *et al.*, 1984; Novilla, 1992). The toxicities of ionophores may be potentiated by other substances and notably by the antimicrobial drug tiamulin (Miller, 1981; Wanner, 1984; Miller *et al.*, 1986; Mitema *et al.*, 1988; Pott, 1990; Bartov, 1994; Wendt *et al.*, 1997; Basaraba *et al.*, 1999; Szucs *et al.*, 2000).

Etorphine (Immobilon), usually in combination with other drugs such as acepromazine or thiopentone, has been used as an analgesic and capture drug in wildlife and other animals. In horses and donkeys, etorphine results in a dramatic rise in blood pressure and heart rate, with pronounced muscle tremors although this can be controlled with the use of other drugs such as thiopentone (Dobbs & Ling, 1972; Hebeler & Budd, 1974; Van Laun, 1977) while its use in fallow dear may lead to fatalities (Low, 1973). Equally poor results have been noted in pigs (and wolves) and other drugs such as azaperone may be safer (Symoens & van der Brande, 1969; Symoens, 1970; Callear & van Gestel, 1973; Tobey & Ballard, 1985; Henrikson *et al.*, 1995).

Fish

Signs of organophosphorus toxicity have been reported in salmon following dichlorvos poisoning and treatment with trichlorfon which is converted to dichlorvos in water; this may also lead to excess residues of the drug in salmon tissues (Horsberg & Høy, 1989; Horsberg *et al.*, 1989,1990). Hydrogen peroxide, also used for the treatment of ectoparasitic disease in fish, may cause gill damage (Clayton & Summerfelt, 1996; Arndt & Wagner, 1997; Kiemer & Black, 1997; Rach *et al.*, 1997; Tort *et al.*, 2002a,b). Ivermectin, which has been used experimentally (and sometimes illegally) to treat sea lice in salmon and other species (Sutherland, 1990; Roth *et al.*, 1993; Palmer *et al.*, 1997) has also caused gill damage after oral and intraperitoneal administration to sea bass (Athanassopoulou *et al.*, 2002). In experimental studies, levamisole proved toxic to Atlantic salmon smolts (Munday & Zilberg, 2003).

Fish vaccines are authorized for a range of species including salmon and trout in areas of northern Europe (Tatner, 1993; Vinitnantharat *et al.*, 1999). These too are generally very safe but adverse injection site reactions may occur with the use of oil-based products (Evensen, 2003).

Off-label use

Many drugs are either used infrequently or are used off-label, usually under the cascade, and consequently they are involved in few adverse reaction reports. For example, with the exception of dogs, cyclosporin is not widely used in veterinary medicine and the numbers of adverse events associated with it are small. Nevertheless, there are a number of cases where adverse reactions have been reported and these involve anorexia, alopecia, vomiting and nausea and hirsutism in dogs and seizures, diarrhoea, anorexia, vomiting and constipation in cats (Ryffel, 1982; Rosenkrantz *et al.*, 1989; Seibel *et al.*, 1989; Kyles *et al.*, 1999; Robson, 2003). Similarly, there are few, if any, antineoplastic drugs authorized for use in veterinary medicine and animals with tumours tend to be treated with products authorized for the treatment of human neoplastic diseases. Hence, agencies such as the VMD are unlikely to receive many, if any, adverse reaction reports. Nevertheless, there are published reports of adverse effects associated with the use of cyclophosphamide, lomustine, 5-fluorouracil and other antineoplastic drugs, in companion animals (Gralla, 1975; Ndiritu & Enos, 1977; Fan *et al.*, 2002; Charney *et al.*, 2003). Studies in healthy dogs suggest that depression of haematopoiesis may be a major concern with cyclophosphamide (Jalil & Pandey, 1987), while hepatotoxicity has been reported with lomustine chemotherapy (Kristal *et al.*, 2004).

ENVIRONMENTAL EFFECTS

Medicines are used systematically in aquaculture. These generally take the form of antibiotics for bacterial infections, antifungal drugs, some of them unauthorized and ectoparasitic drugs to combat parasitic infections, particularly sea lice in farmed salmon (Alderman & Clifton-Hadley, 1988; Brown, 1989; Inglis *et al.*, 1993; Roth *et al.*, 1993; Burka *et al.*, 1997). The products used may be either liquid formulations or those integrated into fish feed. Either way, they are used in the

aquatic environment such as rivers (e.g. in trout farming), sea lochs (e.g. in salmon farming), or in coastal waters (e.g. in cod farming). In all cases, excess medicinal product, either direct from liquid formulations or leachate from medicated feed, may spread out from the site of treatment (Boxall *et al.*, 2002,2003a,b). In addition, materials arising from fish excreta also provide a pollution risk (Liao, 1970).

One of the major economic and animal welfare problems associated with salmon farming is sea lice (Thomassen, 1993). These are ectoparasitic copepods including *Lepeophtheirus salmonis* and *Caligus elongatus* which feed on the skin of Atlantic salmon, *Salmo salar*. They cause economic and welfare problems in farmed fish (Richards, 1983; Roth *et al.*, 1993). Several products containing a number of compounds have been used to treat this condition in the UK, including azamethiphos, dichlorvos, hydrogen peroxide, emamectin benzoate, cypermethrin and diflubenzuron (Roth *et al.*, 1993; Thomassen, 1993; Burka *et al.*, 1997; Bishop, 1998; Anon., 2002). Prior to authorization, these medicines have had to be tested for potential adverse environmental effects, but attempts have been made to monitor their impact once in use (Bell, 1995; Woodward; 1996). A recent report has identified two sea lice medicines as priorities for study – cypermethrin and emamectin benzoate at four fish farms in Lochs Craignish, Sunart, Diabaig and Kishorn. Major components of the ecosystem were examined including benthic meiofauna, inter-tidal organisms, sublittoral organisms, benthic macrofauna, zooplankton and phytoplankton. The study is unlikely to be completed before late 2004 but thus far, the authors have not 'observed any catastrophic perturbation of the sea lochs' studied (Scottish Association for Marine Science, 2003). Emamectin benzoate has been shown to have a favourable environmental profile while being extremely effective in controlling sea lice (Stone *et al.*, 1999; Willis & Ling, 2003).

Environmental release of drugs from companion animals is likely to be minimal (Boxall *et al.*, 2002). However, domestic users, farmers and veterinary practices could conceivably dispose of unused or unwanted medicines in such a way that the environment could be compromised, and some substances used in veterinary medicines are known to be toxic to aquatic animals and plants (Burridge *et al.*, 1999; Halling-Sørensen *et al.*, 2000; Halling-Sørensen, 2000). These include synthetic pyrethroids such as flumethrin and deltamethrin and organophosphorus compounds such as diazinon and chlorfenvinphos. Substances used as active ingredients in aquaculture products such as emamectin benzoate, hydrogen peroxide, azamethiphos and cypermethrin have been extensively studied as part of the authorization process and although potentially hazardous, should not cause any undue risks when used according to the label instructions.

Compounds like diazinon are highly toxic to earthworms and other terrestrial organisms as well as to bees (Vink *et al.*, 1995; Larkin & Tjeerdema, 2000). Concern has been expressed over the toxicity of the avermectin endectocides used widely in large animal veterinary medicine. These include ivermectin and doramectin, and the related compound moxidectin (a milbemycin). Avermectins and milbemycins have given rise to this concern as they are voided from the animal in the faeces where they may continue to exert their insecticidal effects. Hence, there has been speculation as to whether they might cause major environmental problems, not only due to their potential effects on insect populations but also because they might prevent the biodegradation of animal dung (Strong & Brown, 1987; Strong, 1993; Doherty *et al.*, 1994; Strong & Wall, 1994; Floate, 1998; Taylor, 1999). The avermectins have low toxicity to a wide range of terrestrial invertebrates and they possess low phytoxicity (Halley *et al.*, 1993). The results of a number of experimental studies have indicated adverse effects on dung fauna by avermectins such as ivermectin and abamectin, whereas levamisole, moxidectin, tiamulin, olaquindox, metronidazole and some of the benzimidazole anthelmintics including fenbendazole and albendazole appear to have no significant adverse effects; there is evidence to suggest that sustained bolus formulations may offer greater risks than other modes of administration (Wall & Strong, 1987; Houlding *et al.*, 1991; Herd *et al.*, 1993; Sommer *et al.*, 1993; Strong & James, 1993; Strong *et al.*, 1996; Wardhaugh & Mahon, 1998; Floate, 1999; Errouissi *et al.*, 2001; Wardhaugh *et al.*, 2001a,b Svendsen & Butler, 2002; Jensen *et al.*, 2003). There is also some evidence to suggest that dung from treated animals may be less attractive to dung fauna, but the reasons for this are unknown (Holter *et al.*, 1993). Treatment with ivermectin might also contribute to reductions in phosphorus recycling but the evidence for this is limited (King, 1993). The concentrations of residues of ivermectin in dung pats are slow to decline (Sommer & Steffanson, 1993). Other investigators have found no or little evidence for adverse effects of avermectins on dung fauna or on dung pat degradation (Barth *et al.*, 1993, 1994; Wratten *et al.*, 1993).

The issue of avermectins and their environmental effects is a controversial area (McCracken, 1993; Ridsdill-Smith, 1993; Herd, 1995, 1996; Forbes, 1996; Wardhaugh & Ridsdill-Smith, 1998). The treatment of terrestrial animals for parasite control is seasonal, as is the breeding of dung fauna. The latter might be at less risk if the breeding season and the treatment seasons are separate, but there may be some degree of risk if coincidental, and the concentrations found may depend on a number of factors including the diets of the treated animals (Ridsdill-Smith, 1993; Cook *et al.*, 1996; McKellar, 1997; Lumaret & Errouissi, 2002), and not all cattle in a herd will necessarily be treated simultaneously (Roncalli, 1989). Interestingly, the original environmental impact assessments of avermectins in the United States took into account patterns of use, their toxicity, metabolic characteristics, predicted environmental concentrations and behaviour in the environment but no consideration was given to effects on dung pat degradation or dung fauna (Bloom & Matheson, 1993). There are some parallels with the treatment of cattle using deltamethrin. Depending on the time they are treated, and their frequency of drug administration, the effects on insects in cattle dung were either negligible or significant. For example, concentrations in faeces after a therapeutic treatment were sufficient to kill adult dung beetles (Wardhaugh *et al.*, 1998). Nevertheless, attempts to control parasitic flies by treating them with avermectins so that residues in dung exert

a beneficial insecticidal effect have met with little or no success (Mahon & Wardhaugh, 1991; Cook, 1993; Floate *et al.*, 2001; Wardhaugh *et al.*, 2001c).

An unusual environmental issue has arisen in Pakistan. Here, there has been a dramatic decline in the numbers of Oriental white-backed vultures (*Gyps bengalensis*) and in other vulture species. In one area, the decline in the Oriental white-backed vulture has been in the region of 95% since the 1990s (Prakash, 1999). The declines were matched by findings of renal failure and visceral gout in affected animals. This correlated with findings of high concentrations of the nonsteroidal anti-inflammatory drug diclofenac, and the ability of diclofenac to reproduce the effects in the birds. It was hypothesized that the morbidity and mortality in the vultures was due to the animals scavenging on dead livestock which had been treated with diclofenac prior to death. Diclofenac is available as an over the counter veterinary drug in Pakistan and is widely used (Oaks *et al.*, 2004).

DISCUSSION

Not surprisingly, many of the adverse effects noted in animals can be directly associated with the toxicological and pharmacological properties of the drug. Thus the gastrointestinal effects of the nonsteroidal anti-inflammatory drugs in dogs, the effects of pyrethroids in cats, and the toxicity seen with certain organophosphorus-based medicines in fish arise from the properties of the compounds concerned and so to a large extent, they are predictable.

Hypersensitivity reactions and anaphylaxis are idiosyncratic in nature. In animals, they occur with some groups of compounds known to induce these effects in humans. These include certain antimicrobial drugs, notably the tetracyclines in dogs and the β-lactam antibiotics in horses.

Not surprisingly, off-label uses, in species which have not been the subject of rigorous pharmaceutical testing with the drug administered, have resulted in adverse reactions in animals.

The potential environmental effects of veterinary medicines are of concern because some may enter the environment directly (e.g. run-off from sheep dips and medicines used in aquaculture). Others pose an indirect threat from the excreta of treated animals, particularly when theses are farmed (and treated) in large numbers. The limited evidence available suggests that the impact of fish medicines, certainly when used judiciously, is small. While experimental data clearly demonstrate that some substances such as the avermectins can harm important organisms, the evidence that they inflict severe environmental damage is limited. Although absence of evidence is not synonymous with absence of effect, it seems likely that the relatively small amounts of drugs used, in conjunction with the environment's capacity to safely absorb them, significantly mitigates the magnitude of any risk they may offer.

Together with the evidence from spontaneous reporting schemes, the available evidence suggests that the frequencies of adverse reactions to veterinary medicines are relatively low although under reporting, as with adverse reactions to human medicines, must be acknowledged. However, the magnitude of any under reporting is difficult to quantify. The adverse reactions that do occur must be seen against the benefits of drug treatment, and the consequences of not treating sick animals or animals at significant risk of becoming sick if prophylactic treatments are withheld.

The value of information available in the literature would be enhanced if it could be seen in conjunction with data generated by spontaneous reporting schemes. Unfortunately, much of the latter is published in anonymized form where not only have the details of the manufacturer been obscured, but so too have the details of the pharmacologically active substance (Woodward, 2005). A higher degree of transparency in these reports would facilitate a broader understanding of the nature of adverse reactions in the veterinary context. Pharmacoepidemiological studies are frequently expensive to conduct thus limiting their utility in the investigation of adverse effects in veterinary medicine. Nevertheless, where these have been conducted, the results have provided valuable insights into the nature of the drugs of interest.

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