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# Influence of febrile disease on the pharmacokinetics of veterinary drugs

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**Summary** — In mammals, tissue damage, inflammation or invasion of pathogenic microorganisms induces systemic changes, collectively known as the 'acute phase response'. Among the varied alterations, which together produce this response, are: fever, inappetence, inhibition of gastric function, synthesis of hepatic acute phase proteins and changes in blood flow to various organs. The intensity of these different reactions may vary depending upon the type of invading microorganism or bacterial toxin given. Considerable attention has been paid to the involvement of pyrogenic cytokines derived from reticuloendothelial cells and phagocytes in the host responses to infection. These cytokines include interleukins, interferons and tumor necrosis factor. In the present paper, attention has been focused on the role of cytokines and the effects of the acute phase response on drug disposition in disease states (including the effect of anorexia on medicated feed intake and drug bioavailability). From the disease-induced changes in pharmacokinetics, it follows that more attention should be paid to drug disposition in patients in relation to efficacy, side effects and drug residues in food products. In relation to good veterinary practice, it is also recommended that the route of administration, dosage and withdrawal time be adjusted according to the severity of the disease.

**disease / pharmacokinetics / fever / dosage regimen / efficacy / withdrawal time**

**Résumé** — **Influence des maladies fébriles sur la pharmacocinétique des médicaments vétérinaires.** Chez les mammifères, les lésions cellulaires, les inflammations et les infections par des micro-organismes pathogènes induisent des modifications systémiques dénommées collectivement sous le terme de «réponse primaire». Parmi les modifications qui participent à cette réponse on retrouve la fièvre, l'inappétence, l'inhibition des fonctions gastriques, la synthèse de marqueurs (protéines hépatiques) et des altérations du débit sanguin régional. L'intensité de ces différentes réactions varie avec le type de micro-organisme ou de la toxine bactérienne. Une attention particulière a été portée aux cytokines pyrogènes produites par les cellules réticuloendothéliales et les phagocytes. Ces cytokines comprennent les interleukines, les interférons et les facteurs de nécrose tumorale. Le présent article précise le rôle des cytokines et les effets de la réponse primaire sur la disposition des médicaments dans les états pathogènes (y compris les effets de l'anorexie sur l'ingestion des aliments médicamenteux et sur la biodisponibilité des médicaments). Compte tenu des modifications pharmacocinétiques induites par les processus pathogènes, une attention particulière doit être portée sur l'efficacité et les effets secondaires des médicaments et sur la présence de résidus dans les tissus consommables. En relation avec les bonnes pratiques vétérinaires, il est également recommandé que la voie d'administration, la posologie et le délai d'attente soient modulés en fonction de la sévérité de la maladie.

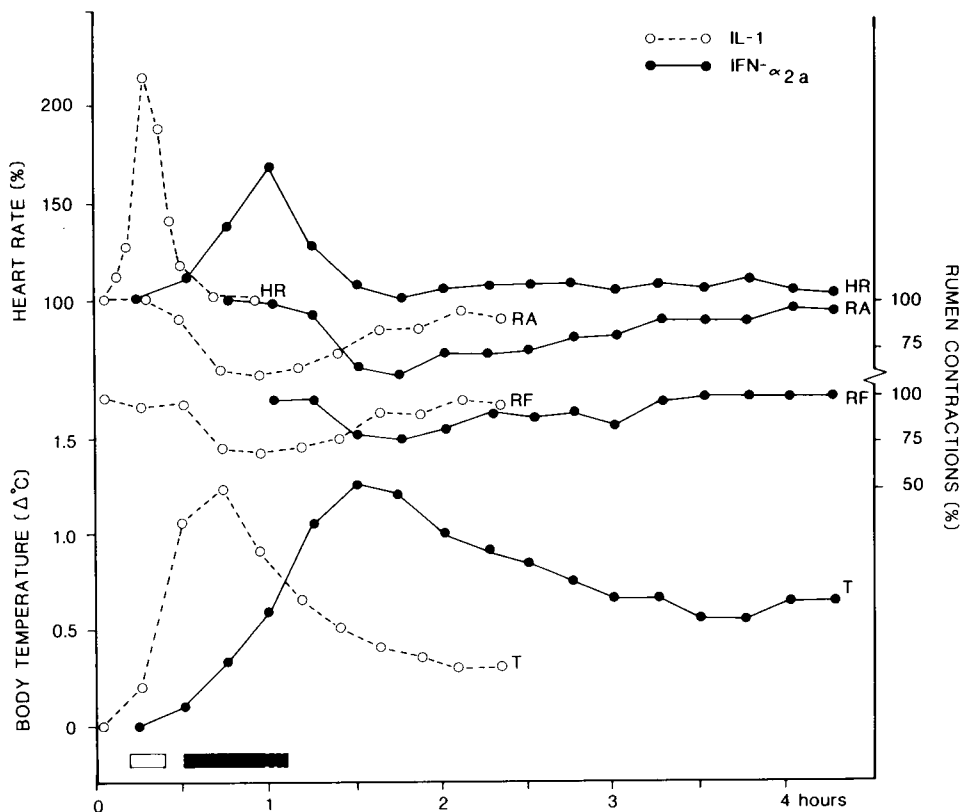
**maladie / pharmacocinétique / fièvre / posologie / efficacité / délai d'attente**

## INTRODUCTION

In mammals, tissue damage, inflammation or invasion of pathogenic microorganisms induces systemic changes, collectively known as the acute phase response. Among the varied alterations, which together produce this response, are: fever, increased lassitude or sleep, inappetence, inhibition of gastric function, tachycardia, a negative nitrogen balance, synthesis of hepatic acute phase proteins, activation of lymphocytes, neutrophilic leukocytosis, mobilization of phagocytes, decreased plasma iron and zinc levels, and changes in the metabolism of carbohydrates, lipids and proteins (Beisel, 1984; Dinarello, 1984, 1985; van Miert, 1985, 1987; Lohuis *et al*, 1988). The intensity of these different reactions may vary depending upon the type of invading microorganism or bacterial toxin given (van Miert and van Duin, 1974, 1979; van Miert *et al*, 1982, 1983b, 1984a, 1984b; Koot *et al*, 1989; Lohuis *et al*, 1989). Therefore, the effect of the acute phase response upon the pharmacokinetic behavior of a drug is not standardized (Abdullah and Baggot, 1986). Over the last three decades, considerable attention has been paid to the involvement of cytokines derived from reticuloendothelial cells and phagocytes in the host responses to infection. These cytokines include interleukins (IL-1, IL-2, IL-6), interferons (IFN $_{\alpha}$ , IFN $_{\beta}$ , IFN $_{\gamma}$ ) and tumor necrosis factor (TNF $_{\alpha}$ , TNF $_{\beta}$ ) or cachectin (Dinarello, 1984; Kluger, 1986; Beutler and Cerami, 1986; Dinarello *et al*, 1988a, 1988b; Tracey *et al*, 1989). Once released into the circulation, these pyrogenic cytokines travel from peripheral sites of infection, inflammation or injury to the brain, where they act on structures in the thermoregulatory center of the hypothalamus to initiate fever. TNF causes

fever through a direct effect on this center, and through induction of IL-1 biosynthesis (Dinarello *et al*, 1986, 1988b). By itself, neither IFN $_{\alpha}$  nor IFN $_{\beta}$  induces IL-1 (Ackerman *et al*, 1984; Dinarello *et al*, 1984), however, IL-1 induces IFN $_{\beta}$  (Dinarello *et al*, 1988b). Nevertheless, it is clear that IFN $_{\alpha}$  is an endogenous pyrogen and induces fever *via* the same mechanism as that shown for IL-1: synthesis of brain prostaglandin E $_2$  (PGE $_2$ ) (Milton, 1982; Coceani *et al*, 1986, 1988; Nakamura *et al*, 1988). In dwarf goats, both IL-1 (crude preparation) and recombinant human IFN $_{\alpha 2a}$  induced shivering, monophasic febrile responses, tachycardia and a slight inhibition of forestomach contractions (fig 1). Intravenous infusion of endotoxin, a potent IL-1- and TNF-inducer (Dinarello, 1984; Beutler *et al*, 1985), caused marked increases in the plasma levels of prostaglandins in rabbits and sheep (Philipp-Dornston and Siegert, 1974; Emau *et al*, 1985; Lohuis *et al*, 1988). In goats, iv infusion of PGE $_2$  induced tachycardia and a moderate inhibition of forestomach contractions, whereas intracerebroventricular injection of PGE $_2$  caused vasoconstriction, intense shivering, a sharp increase in body temperature, and a longer-lasting inhibition of ruminal contractions (Veenendaal *et al*, 1980; van Miert *et al*, 1983a). Thus, there is considerable evidence that PGE $_2$  is the major arachidonic metabolite associated with rises of the hypothalamic thermostat to febrile levels. Furthermore, these results suggest that both fever and inhibition of forestomach contractions result from PGE $_2$  interference with receptors in the same region of the brain.

In the present article, attention will be focused on the effects of the acute phase response on drug pharmacokinetics in disease states.



**Fig 1.** Changes in heart rate (HR), rumen motility (RF and RA) and body temperature (T) of dwarf goats after iv infusion of crude interleukin-1 (O: 5 ml/kg body weight equivalent to  $2 \times 10^8$  leukocytes/kg;  $n = 4$ ) and recombinant human interferon- $\alpha_{2a}$  (●:  $5 \times 10^4$  IU/kg body weight;  $n = 5$ ). Heart rate and rumen contractions are expressed as percentages of the preadministration values; RF = frequency of contraction/15 min; RA = summation derived from 15 min intervals of amplitude. Only mean values are shown. Horizontal bars (IL-1 open; IFN $\alpha_{2a}$  black) indicate periods of intense shivering (partly based on van Miert and van Duin, 1974).

**FEBRILE ANOREXIA, MEDICATED FEED INTAKE AND DRINKING WATER CONSUMPTION**

One of the more common signs of febrile diseases is inappetence (Phillips, 1984; van Miert *et al*, 1986; Langhans and Scharrer, 1986; van Miert, 1987). In labo-

ratory animals, pyrogenic cytokines, such as IL-1 (McCarthy *et al*, 1985a, b; 1986; Otterness *et al*, 1988; Plata-Salaman *et al*, 1988) and TNF (Plata-Salaman *et al*, 1988; Kettelhut and Goldberg, 1988; Socher *et al*, 1988; Tracey *et al*, 1988; Grunfeld *et al*, 1989), suppress feed intake, whereas the therapeutic use of IFN $\alpha_{2a}$  in man in-

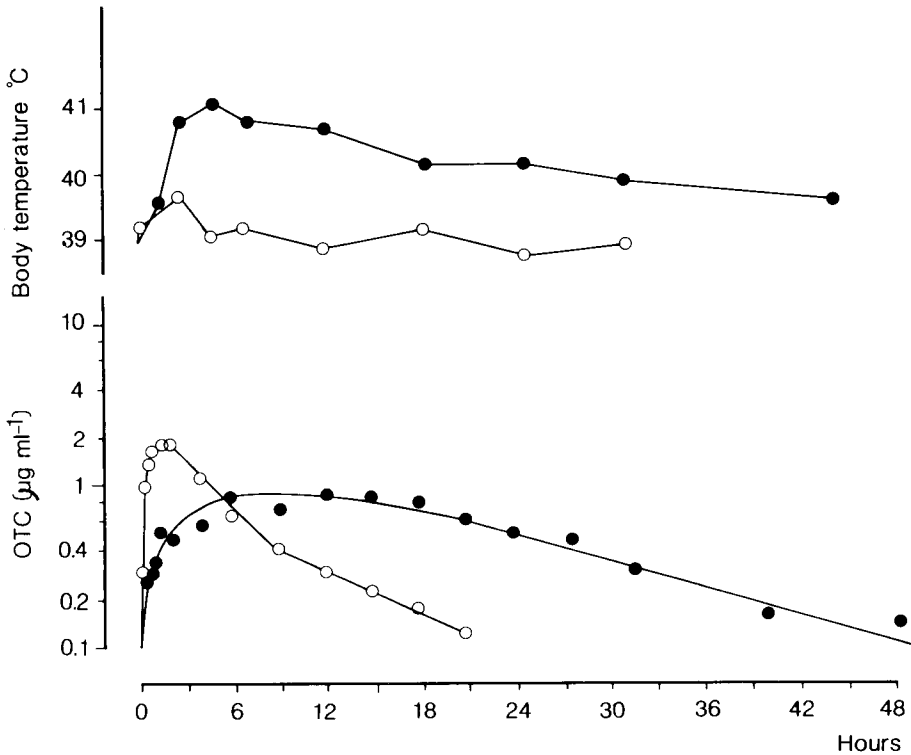
duces side effects including fever and inappetence (Fent and Zbinden, 1987). In dwarf goats, iv injection of IFN-inducers and im injection of human recombinant (hr) IFN- $\alpha_{2a}$  both resulted in increased rectal temperatures and significant reductions in feed consumption (Koot *et al*, 1988, 1989). Similar results were obtained after iv injection of *Escherichia coli* endotoxin (Baile *et al*, 1981; van Miert *et al*, 1986), which is a potent IL-1 and TNF inducer (Dinarello, 1984; Beutler *et al*, 1985). However, appetite suppression has been shown to be independent of PGE<sub>2</sub> induction (McCarthy *et al*, 1984; van Miert *et al*, 1986; Kettelhut and Goldberg, 1988; O'Reilly *et al*, 1988). Interestingly, anorexia in gastrointestinal helminth infection seems to be mediated by increased cholecystokinin secretion (Symons and Hennessey, 1981). Cholecystokinin is one of the hormones controlling appetite (de Jong, 1987). Although the exact mechanisms are still unknown, febrile anorexia may complicate the oral treatment of patients suffering from acute infectious diseases. Therefore, we studied feed intake and water consumption in pigs before and after infection with *Haemophilus (Actinobacillus) pleuropneumonia*. Infection and iv injection of *H pleuropneumonia* toxins (Pijpers *et al*, 1990) both resulted in fever (fig 2), anorexia and significant reductions in drinking water consumption (fig 3). These results suggest that disease states may have a negative influence on medicated feed intake and on medicated water consumption. Therefore, parenteral drug administration is to be preferred in these patients.

### FEBRILE CONDITIONS AND DRUG BIOAVAILABILITY

Parenteral injection of exogenous pyrogens, such as staphylococcal enterotoxins

(van Miert *et al*, 1983b, 1984b), endotoxins from *E coli* or *Salmonella typhimurium* (van Miert *et al*, 1977, 1982), Newcastle's disease virus (van Miert and van Duin, 1974), poly I:poly C (van Miert and van Duin, 1979; Koot *et al*, 1989), hr IFN- $\alpha_{2a}$  (Koot *et al*, 1989), sodium nucleinate from yeast (van Miert and van Duin, 1979), or johnin challenge after vaccination with *Mycobacterium johnei* (van Miert and van Duin, 1974), induced fever, changes in heart rate and inhibition of forestomach contractions, although there were differences in latency time, the shape of the temperature curves and the shape of the rumen motility curves. Similar observations have been made in goats infected with tick-borne fever (van Miert *et al*, 1984a) and *Trypanosoma vivax* (Veenendaal *et al*, 1976), or cattle infected with bovine ephemeral fever (Burgess and Spradbrow, 1977; Uren and Murphy, 1985) or with *E coli* mastitis (Lohuis *et al*, 1989).

In monogastric species, the first observations in this field appear to be those of Meyer and Carlson (1917) and Meyer *et al* (1918). They observed that dogs with distemper or pneumonia refused food and showed complete atony of the stomach with absence of hunger contractions. In addition, they performed some experiments in which fever was evoked by pyrogens, such as sodium nucleinate and a killed culture of *Serratia marcescens*. The authors concluded that gastric secretion and hunger contractions were absent in marked fever and that these effects were associated with anorexia as long as the fever was present. Since that time, other investigators have confirmed these observations, although the exact mechanisms involved are still unknown. In our experiments with rats, *E coli* endotoxin induced inhibition of gastric secretion and gastric emptying rate (table I). Pretreatment with non-steroidal anti-inflammatory agents, which inhibit prosta-

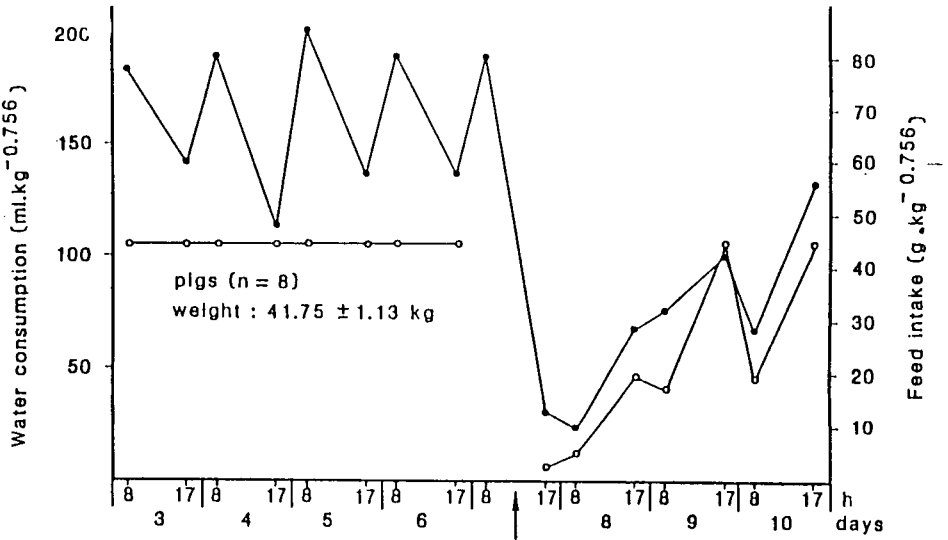


**Fig 2.** Mean concentrations of oxytetracycline (OTC,  $\mu\text{g/ml}$ ) in plasma of pigs ( $n = 8$ ) following oral administration of the drug (50 mg/kg body weight) on an empty stomach with (●), or without (○) *Actinobacillus pleuropneumonia* toxin-induced fever. Mean body temperature responses are shown in the upper curve (Pijpers *et al*, 1990).

glucan synthesis, was ineffective to antagonize these endotoxin-induced effects (van Miert and van Duin, 1980).

Although the stomach is not itself an important site of drug absorption, the rate of gastric emptying can markedly influence the rate of intestinal drug absorption. Furthermore, the gastric pH increase during endotoxin-induced fever is important, as the solubility of some drugs, such as tetracyclines, is reduced with increasing pH (van Miert, 1983). Several investigators

have reported that the rates of drug absorption after oral administration to veal calves (Groothuis *et al*, 1978), pigs (Ladefoged, 1979a) and rabbits (Ladefoged, 1978a, 1979b) were reduced during endotoxin-induced fever. In pigs, we recently studied the effect of *Haemophilus* (*Actinobacillus*) *pleuropneumonia* (HPP) toxins on the rate of oxytetracycline absorption administered on an empty stomach (fig 2). During the febrile state, the maximal concentration of oxytetracycline in plasma was



**Fig 3.** Feed intake (g/kg<sup>0.756</sup>) and water consumption (ml/kg<sup>0.756</sup>) in pigs (n = 8) before and after (↑) injection of *A pleuropneumonia* toxins. The animals were fed 750 g of pelleted concentrate twice daily; water was provided *ad libitum* (Pijpers *et al*, 1990).

**Table I.** The effect of *E coli* endotoxin (LPS) on gastric function in the rat.

	Saline	LPS (0.1 µg/100 g bw)
<b>Gastric secretion</b>		
number of rats	9	9
volume (ml/kg bw)	27 ± 3	12 ± 1 <sup>b</sup>
pH	2.4 ± 0.7	4.8 ± 0.6 <sup>b</sup>
acid output (meq/100 g bw)	218 ± 31	59 ± 8 <sup>b</sup>
acid concentration (meq/l)	80 ± 7	53 ± 13 <sup>b</sup>
<b>Gastric emptying rate</b>		
number of rats	36	39
retention (%) <sup>a</sup>	19 ± 4.7	81 ± 4.0 <sup>b</sup>

Parameters for secretion and emptying rate were determined 3 h after intravenous LPS administration (in the controls: saline 0.1 ml/100 g bw). Mean values ± SEM are given (based on Leenen and van Miert, 1969; van Miert and de la Parra, 1970; van Miert and van Duin, 1980).

<sup>a</sup> Number of beads as the percentage of the number of beads administered (gelatin capsules no 5, filled with 20 stained glass beads (2 x 1 mm) each).

<sup>b</sup>  $P < 0.05$ ; Wilcoxon's two sample test.

attained 4 times more slowly than during the healthy state ( $T_{\max}$  in h:  $7.00 \pm 1.5$  vs  $1.74 \pm 0.53$ ), whereas the mean plasma peak concentration was twice as low as the corresponding concentration in the control experiment ( $C_{\max}$  in mg/l:  $0.87 \pm 0.45$  vs  $1.87 \pm 0.29$ ). Furthermore, the elimination half-life of the drug was prolonged after HPP toxin administration ( $t_{1/2\beta}$  in h:  $14.12 \pm 5.83$  vs  $5.92 \pm 1.09$ ); due to the increased  $t_{1/2\beta}$ , area under the curve (AUC) values were significantly higher (AUC in mg/h/l:  $26.2 \pm 12.7$  vs  $13.7 \pm 3.3$ ). The clinical significance of delayed absorption depends upon the circumstances. It may be important if rapid onset of action is required or if elimination is so rapid that effective plasma concentrations cannot be achieved. Also, some drugs, such as erythromycin, are degraded in the stomach and if emptying is delayed, the amount of active drug available for absorption is reduced. To avoid any detectable drug residue in meat, withdrawal times should be increased in cases similar to those described above (in our pig experiment at least 3 times).

Endotoxins (Beutler *et al*, 1985) and staphylococcal enterotoxins (Tracey *et al*, 1989) are potent inducers of TNF. Beutler and Cerami (1986) suggested that the enhanced TNF concentrations in plasma might be responsible for the various pathological effects observed during endotoxemia, including diarrhea. The goat is a species very susceptible to intravenous staphylococcal enterotoxin-B (van Miert *et al*, 1983b, 1984b). Among other changes, this toxin induces fever, anorexia, inhibition of forestomach contractions and profuse watery diarrhea. The ruminal stasis and watery diarrhea had a profound negative effect on the oral bioavailability of sulfadimidine (van Gogh *et al*, 1984). In the swine industry, most drugs are administered orally and there is remarkably little information on the effects of diarrhea on their absorp-

tion. Therapeutic failure is less spectacular than drug toxicity and is more likely to go unnoticed by practitioners. It may be due to failure of sufficient absorption of the administered drug. Therefore, parenteral drug administration is to be preferred in these cases.

During rising fever, blood flow in sheep and goats shifts away from heat loss tissues (*eg*, skin) to heat production tissues (*eg*, shivering muscles) (van Miert *et al*, 1983a), whereas cardiac output increases (Blatteis *et al*, 1988). During rising fever, induced with *E coli* endotoxin, the rate of absorption of ampicillin from shivering muscles was faster, resulting in significantly higher serum concentrations of the antibiotic than in control non-febrile goats (Groothuis *et al*, 1980). In contrast, the absorption rate of ampicillin from non-shivering muscles (*eg*, neck muscles) was slower, resulting in significantly lower serum concentrations of the antibiotic than in control non-febrile veal calves (Groothuis *et al*, 1978). On the basis of these findings, it is difficult to speculate on the effect 'clinical' fever may have on the efficacy of antibiotic suspensions in disease states. Endotoxin-induced fevers are of rather short duration in contrast to fevers observed during natural infections caused by Gram-negative bacteria such as *Salmonella* and *Pasteurella* species.

## FEBRILE CONDITIONS AND DRUG DISTRIBUTION

Distribution is a physicochemical interaction between a drug and the body. Therefore, the pattern of this distribution is determined by the properties of these two partners. On the one hand, the physicochemical properties of the drug, such as  $pK_a$  value or ionization degree, lipid solubility or polarity and molecular weight, play a



major role. On the other hand, factors, such as pH values, tissue composition, permeability of membrane barriers, blood flow and capillarization of the body, have the same importance (Benet, 1976; Klotz, 1976). In sheep, the blood flows to most organs of the gastrointestinal system (including the forestomachs) were reduced significantly during endotoxin-induced fever, whereas blood flows increased to the adrenal glands but decreased to the thyroid (Blatteis *et al*, 1988). The change in adrenal blood flow probably reflects the IL-1-induced glucocorticoid production (Besedovsky *et al*, 1986). Physical stress may alter the hydration of the body and subsequently distribution volume. Changes in thyroid function may also be responsible for differences in tissue distribution. Changes in the permeability of membrane barriers and/or tissue-plasma pH may alter the distribution pattern of drugs as well. These changes may be important in patients suffering from infectious encephalitis, prostatitis, arthritis or mastitis. For example, in pony mares with endotoxin-induced arthritis (associated with fever), ampicillin and kanamycin entered the synovial fluid of the inflamed joints more quickly and attained higher concentrations than in the uninfamed joints (Firth *et al*, 1988). In cattle with *E coli* endotoxin-induced mastitis (associated with fever), increased milk/plasma concentration ratios have been reported for weak acidic drugs, such as methicillin (Ziv *et al*, 1983) and amoxicillin (Blanchflower, 1983). For weak basic drugs, decreased milk/plasma concentration ratios have been found (Ziv, 1980).

Although plasma drug concentrations are usually measured as total (free + bound) concentrations, it is only the free non-protein-bound drug that is available to equilibrate with the receptor sites in tissues. Several disease states may alter the

free drug fraction and by doing so may disrupt the usual relationship between total drug concentration and response. Disease states may affect drug protein binding through two main mechanisms: 1) by altering the concentration of protein available for drug binding, and 2) by altering the affinity of drugs for plasma proteins (Perucca *et al*, 1985). The most important drug-binding proteins are albumin and the acute phase reactant  $\alpha_1$ -acid glycoprotein (AGP). AGP binds mainly basic drugs, while albumin is responsible primarily for the binding of acidic drugs. Since serum AGP concentrations frequently increase in response to inflammatory disease, lower free drug concentrations can be measured than in healthy states (Belpaire *et al*, 1987; Dello *et al*, 1988). Impairment in drug binding related to pathological conditions (trypanosomiasis, infections caused by helminths) is often related to hypoalbuminemia (Abdullah and Baggot, 1986). Increases in plasma concentrations of free fatty acids are another important determinant in the albumin binding of acidic drugs. For example, the reduced protein-binding of sulfathiazole in pigs during endotoxin-induced fever might be due to altered plasma concentrations of free fatty acids under these conditions (Friis and Ladefoged, 1979). Moreover, high bilirubin levels can also increase the free fraction of certain highly albumin-bound drugs (Perucca, 1980).

Since many factors can affect drug plasma levels in disease states, one must be very cautious in explaining changes in drug distribution. For example, an increased volume of drug distribution for penicillin G has been reported in dogs suffering from a generalized streptococcal or *Pseudomonas aeruginosa* infection, and for quinine during febrile episodes in patients with malaria. Similar results were found in rabbits, pigs and dogs during en-

dotoxin-induced fever (for a review see van Miert, 1985) and in goats with tick-borne fever (Knoppert *et al*, 1988). On the other hand, pigs, dogs, rabbits and horses showed higher blood concentrations of sulfathiazole, sulfadimidine and gentamicin during endotoxin-induced fever (van Miert, 1985), whereas unchanged drug distribution has been reported in calves suffering from salmonellosis (table II) or pneumonic pasteurellosis (Burrows *et al*, 1986; Groothuis and van Miert, 1987).

### FEBRILE CONDITIONS AND DRUG BIOTRANSFORMATION

During infectious diseases, the liver often shows biochemical and pathological evidence of tissue damage, and therefore the possibility of impaired drug metabolism arises. Several investigators have reported increased parent drug/metabolites ratios during febrile conditions, suggesting impaired hepatic drug metabolism (Song *et al*, 1972; Trenholme *et al*, 1976; van Miert

*et al*, 1976; Anika *et al*, 1986b; van Gogh *et al*, 1989). However, the exact mechanisms involved are not quite clear, since many factors can affect drug biotransformation (Benet, 1976; Ladefoged, 1978b; Thiessen and Poon, 1979). Both inappetence and a change in liver blood flow may alter parent drug/metabolites ratios. It has recently been shown that food deprivation decreased body clearance of certain drugs in horses (Engelking *et al*, 1987) and goats (Abdullah and Baggot, 1988). The reductions in clearance of these compounds were not entirely due to reductions in hepatic blood flow (Engelking *et al*, 1987). After endotoxin injection, sheep showed a decreased hepatic blood flow during the rise in body temperature which remained low at fever peak. However, there was a significant increase in liver flow during the recovery episode (Blatteis *et al*, 1988). These changes may be associated with the increased activity of the reticuloendothelial system under these conditions. In sheep, endotoxin injection increased hepatic oxidation of [<sup>14</sup>C]serine and the net

**Table II.** Some pharmacokinetic parameters for amoxicillin-Na (30 mg/kg iv), trimethoprim (4.5 mg/kg iv), and chloramphenicol (50 mg/kg iv) in healthy and *Salmonella dublin*-infected ( $2 \times 10^7$  bacteria) veal calves.

	$t_{1/2\beta}$ (h)	Cl (l/h/kg)	Vd( $\beta$ ) (l/kg)	AUC (mg/h/l)	n
Amoxicillin control	2.49 $\pm$ 0.06 <sup>a</sup>	0.45 $\pm$ 0.02	0.89 $\pm$ 0.06	73.3 $\pm$ 3.0	5
infected (60 h)	3.35 $\pm$ 0.20 <sup>b</sup>	0.49 $\pm$ 0.01	1.09 $\pm$ 0.04	64.8 $\pm$ 5.6	
Trimethoprim control	1.18 $\pm$ 0.08	1.45 $\pm$ 0.22	2.38 $\pm$ 0.33	3.10 $\pm$ 0.43	5
infected (36 h)	1.63 $\pm$ 0.27 <sup>b</sup>	1.00 $\pm$ 0.12 <sup>b</sup>	2.20 $\pm$ 0.15	4.53 $\pm$ 0.76 <sup>b</sup>	
Chloramphenicol control	7.31 $\pm$ 0.39	0.130 $\pm$ 0.004	1.45 $\pm$ 0.02	346 $\pm$ 11.4	6
infected (60 h)	13.56 $\pm$ 0.62 <sup>b</sup>	0.078 $\pm$ 0.003 <sup>b</sup>	1.38 $\pm$ 0.04	618 $\pm$ 20.9 <sup>b</sup>	

<sup>a</sup> Mean values  $\pm$  SEM. (Partly based on Groothuis and van Miert, 1987.)

<sup>b</sup>  $P < 0.05$ , paired *t* test.

incorporation of [ $^{14}\text{C}$ ]serine carbon and [ $^{14}\text{C}$ ]alanine carbon into hepatic proteins (Southorn and Thompson, 1987). This probably reflects the increased synthesis of hepatic acute phase proteins by pyrogenic cytokines. Apart from these indirect effects, pyrogenic cytokines can also affect hepatic parenchymal cells directly (West *et al*, 1985; Ghezzi *et al*, 1986; Peterson and Renton, 1986a, b).

Hepatic cytochrome P-450 is important in the metabolism of many drugs. Multiple factors, such as ingestion of inducing agents, nutritional state (including development of the forestomach system), treatment with anabolic hormones and liver diseases, influence hepatic levels of cytochrome P-450 (Baggot, 1988; Davey, 1988; van Miert *et al*, 1988; van Miert, 1989). Induction of the acute phase response by endotoxin (Gorodischer *et al*, 1976; Egawa and Kasai, 1979; McGivney and Bradley, 1980; Ghezzi *et al*, 1984, 1986; Shedlofsky *et al*, 1987) or direct administration of cytokines, such as IL-1 (Ghezzi *et al*, 1986; Shedlofsky *et al*, 1987) and IFNs (Ghezzi *et al*, 1984; Descotes, 1985; Taylor *et al*, 1985; Mannering

and Deloria, 1986; Dolphin *et al*, 1987), depresses hepatic cytochrome P-450 activity in laboratory animals. Furthermore, mice infected with *Trypanosoma brucei* showed decreased total hepatic cytochrome P-450 levels and reduced mixed-function oxidase activity (Shertzer *et al*, 1981). There is some evidence which suggests that increased amounts of TNF are produced by the host in response to *T brucei* infection (Rouzer and Cerami, 1980; Beutler *et al*, 1985; Beutler and Cerami, 1986). Moreover, decreased levels of liver cytochrome P-450 have been found in mice after treatment with TNF (Ghezzi *et al*, 1988). Recently, we found decreased sulfadimidine plasma clearances and increased sulfadimidine half-lives in *T brucei*-infected dwarf goats (van Gogh *et al*, 1989).

In human beings, viral upper-respiratory tract infections appear to alter theophylline pharmacokinetics (Chang *et al*, 1978; Renton, 1978), whereas influenza vaccination impaired the elimination of theophylline and amidopyrine metabolism in healthy volunteers (Renton *et al*, 1980; Kramer and McClain, 1981). Although RNA viruses are potent IFN inducers, the administration

**Table III.** Some pharmacokinetic parameters for ampicillin-Na (20 mg/kg iv), trimethoprim (20 mg/kg iv), aditoprim (10 mg/kg iv), chloramphenicol (50 mg/kg iv), sulfadimidine (50 mg/kg iv) and oxytetracycline (10 mg/kg iv) in healthy and tick-borne fever-infected dwarf goats.

	$t_{1/2\beta}$ (h)		Clearance (l/h/kg)	
	before	after (90 h)	before	after (90 h)
Ampicillin	0.92 ± 0.08 <sup>a</sup>	1.10 ± 0.05	0.56 ± 0.03	0.67 ± 0.07
Trimethoprim	0.84 ± 0.06	0.90 ± 0.06	3.11 ± 0.39	3.18 ± 0.76
Aditoprim	8.00 ± 0.31	10.28 ± 0.67 <sup>b</sup>	0.57 ± 0.06	0.64 ± 0.05
Chloramphenicol	1.49 ± 0.16	1.94 ± 0.25 <sup>b</sup>	0.40 ± 0.04	0.36 ± 0.05
Sulfadimidine	2.9 ± 0.31	5.1 ± 0.70 <sup>b</sup>	0.06 ± 0.01	0.02 ± 0.004 <sup>b</sup>
Oxytetracycline	6.1 ± 0.58	7.3 ± 0.33 <sup>b</sup>	0.13 ± 0.01	0.10 ± 0.01 <sup>b</sup>

<sup>a</sup> Mean values ± SEM. (Anika *et al*, 1986a, 1986b; Knoppert *et al*, 1988).

<sup>b</sup>  $P < 0.05$ , paired  $t$  test.

of equine influenza vaccine did not change the elimination of theophylline in horses (Short *et al*, 1986). The authors suggested that the failure of vaccination to substantially increase plasma IFN concentrations, and thereby alter theophylline elimination, was related to the use of an inactivated viral vaccine.

Although most of the drug biotransformation capacity of the liver is contained in the hepatocytes, the status of non-parenchymal cells of the reticuloendothelial system (RES) appears to play an important role in the maintenance of cytochrome P-450 levels in the hepatocytes. Whenever animals are inoculated with microorganisms or agents that are phagocytized by the RES, the level of drug biotransformation in the liver appears to decrease simultaneously (West *et al*, 1985; Peterson and Renton, 1986a). After the process of phagocytosis (*in vivo* or *in vitro*) by Kupffer cells in the liver, a factor is released which depresses cytochrome P-450 and related drug biotransformation in the adjacent parenchymal cells. The loss which occurs by this mechanism – probably due to IL-1 (Ghezzi *et al*, 1986; Shedlofski *et al*, 1987) – is in addition to the loss of cytochrome P-450 and related drug metabolism that occurs following the induction of IFNs (Peterson and Renton, 1986b). Therefore, the decreases in drug biotransformation that occur during infections are likely to occur *via* both mechanisms.

## FEBRILE CONDITIONS AND DRUG EXCRETION

For drugs that are to be administered to food-producing animals, withdrawal times are generally based on pharmacokinetic studies and measurements of drug residues in healthy animals. This is not always acceptable, since pathophysiological con-

ditions may delay the excretion of drugs. Several investigators have shown that renal dysfunction (Nouws and Ziv, 1978; Gallazzi, 1983) and liver damage (Williams and Mamelok, 1980; Davey 1988) may alter the elimination rates of drugs.

First of all, if the rate of drug elimination is abnormal, then the time to reach steady-state (*ie*, about 5 half-lives) may be importantly altered. Furthermore, in patients with renal insufficiency associated with uremia, a marked decrease in the affinity of many acid drugs for plasma albumin has been reported (Perucca *et al*, 1985). Because renal clearance is blood flow-dependent, drug elimination by the kidney can be impaired when reduced cardiac output compromises renal blood flow. Fortunately, creatinine and inulin clearances provide valuable indicators of the efficacy of elimination for many drugs that are primarily excreted by the kidneys. In sheep treated with *Salmonella typhi* endotoxin, cardiac outputs rose significantly during rising fever but were near basal levels at fever peak and during the recovery period. Renal blood flow was unchanged during fever but was significantly reduced during the recovery period (Blatteis *et al*, 1988). In dogs, *Pseudomonas* endotoxin induced fever, tachycardia, increased total renal blood flow and polyuria, whereas cardiac output and creatinine clearance were not significantly altered. Despite increased renal blood flow, distribution of blood flow within the renal cortex did not change significantly during fever (Cronenwett and Lindenauer, 1979). In spite of the unchanged inulin clearance, pigs showed a marked decrease in sulfathiazole clearance during *E coli* endotoxin fever (Friis and Ladefoged, 1979). In addition to glomerular filtration, both active tubular secretion and back diffusion are involved in the renal handling of this drug. In goats infected with tick-borne fever, renal tubular function was impaired to the extent that sulfadimidine

metabolites normally secreted by renal tubules were retained in plasma (van Gogh *et al*, 1989). Moreover, the glomerular filtration rate, as monitored by creatinine clearance, was diminished in these goats. Furthermore, there was additional evidence of renal dysfunction in some animals which had azotemia and dilute urine (Watson *et al*, 1988). A low urine flow and a shift to a more acidic pH favor the passive tubular reabsorption of lipophilic weak acids. In tick-borne fever-infected goats, urine pH varied between 5.5 and 6.5, while urine pH was approximately 9 before inoculation (van Gogh *et al*, 1989). These findings might explain the reduced sulfadimidine plasma clearance and the associated increased plasma half-life of the drug in affected goats (table III). In pigs treated with endotoxin, urine pH tended to be more acidic as well, whereas urine flow was unchanged (Friis and Ladefoged, 1979). On the basis of these different data, it is difficult to speculate on the effect 'clinical' fever may have on renal function. At the present time, sufficient data are not available to permit a clear understanding of how fever (pyrogenic cytokines) affects drug excretion.

## CONCLUSIONS

From the 'acute phase response'-associated changes in pharmacokinetics, it follows that more attention should be paid to the disposition of a drug in patients in relation to its efficacy, drug-induced side effects and residues of the parent compound and its metabolites in food products. We have now reached the stage in the control of animal disease where more thought must be given by the practitioner to the proper use of the range of drugs in all fields of disease control. Because there is often relatively poor communication be-

tween scientists, practitioners and farmers, misuse of drugs is possible and this can lead to ill-informed criticism of the value of therapy in the veterinary field by public health and medical authorities. It is important now to ensure that, where possible, effective routines of therapy are properly defined for all the major disease areas, so that it will be clear both to the farmer and to the veterinarian how drugs should be used and how it is possible to minimize both the dangers of drug resistance in farms and the likelihood of persistent tissue residues in meat, milk and eggs sold for human consumption (Brander, 1982). Good practices in the use of veterinary drugs means the selective and proper usage including withdrawal periods – approved by national authorities – of authorized veterinary drugs under practical conditions after a proper diagnosis has been made (based on anamnesis and clinical investigation (van Miert, 1988)). From the disease-induced changes in pharmacokinetics, it follows that, in relation to good veterinary practice, route of administration, dosage and withdrawal time should be adjusted according to the severity of the disease.

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