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PHARMACOKINETICS OF PRALIDOXIME IN *BUBALUS BUBALIS*

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SUMMARY

Pharmacokinetics of pralidoxime (2-PAM) and its effect on blood enzymes were investigated in male buffalo calves following single intravenous administration (15 mg/kg). The distribution half-life, elimination half-life, apparent volume of distribution and total body clearance were $0{\cdot}086 \pm 0{\cdot}001$ h, $2{\cdot}36 \pm 0{\cdot}09$ h, $1 \pm 0{\cdot}05$ l/kg and 296 ± 13 ml/h/kg, respectively. The drug plasma levels $\geqslant 4$ μg/ml were maintained up to 3 h. 2-PAM significantly elevated the serum carboxylesterase and lowered the serum levels of aspartate aminotransferase, alanine aminotransferase, acid phosphatase, alkaline phosphatase and lactate dehydrogenase.

INTRODUCTION

Pralidoxime chloride (2-pyridine aldoxime methochloride; 2-PAM chloride) is a cholinesterase (ChE) reactivator used widely against organophosphate intoxication in man and animals (Taylor, 1980; Hatch, 1982). The repeated administration of ChE reactivator at suitable time intervals as determined from its pharmacokinetic studies is necessary for successful therapy. Although the pharmacokinetics of 2-PAM have been extensively investigated in man and animals (Jager *et al.*, 1958; Sidell & Groff, 1971; Swartz & Sidell, 1974; Das Gupta *et al.*, 1979), such studies are lacking in buffalo species. In the present study, we have investigated the pharmacokinetics of 2-PAM and its effect on various blood enzymes in male buffalo calves after single intravenous administration.

MATERIALS AND METHODS

Animals

Healthy male buffalo calves weighing between 75 and 80 kg were used. The animals were adapted to laboratory conditions for 2 weeks prior to commencement of experiments. The calves were maintained on a standard ration and were supplied with water *ad libitum.*

Administration of 2-PAM and collection of blood samples

Pralidoxime chloride (Aldrich Chemical Co., Milwaukee, WI) was administered in isotonic saline into the left jugular vein at a dose level of 15 mg/kg body weight. The dose of reactivator refers to base. Blood samples were drawn by right jugular venepuncture

before and at several times after injection of 2-PAM. Erythrocytes, plasma and serum were separated soon after their collection at room temperature.

Analytical procedures

The concentrations of 2-PAM in plasma were determined by spectrophotometry (Dultz *et al.*, 1957). Erythrocyte and plasma cholinesterases were measured by the method of Fleisher, Pope & Spear (1955) as modified by Sharma, Shupe & Potter (1973). Serum carboxylesterase was determined by using indophenyl acetate as the substrate (Mendoza, Shields & Phillips, 1971). Aspartate aminotransferase, alanine aminotransferase, acid phosphatase, alkaline phosphatase and lactate dehydrogenase were estimated in serum as described by Wootton (1964).

Analysis of data

The plasma concentration-time profile of 2-PAM for each experimental animal was used to calculate various pharmacokinetic parameters (Gibaldi & Perrier, 1975). Statistical significance of biochemical parameters was tested by Student's *t*-test.

RESULTS AND DISCUSSION

The mean plasma levels of 2-PAM plotted on a semilogarithmic scale as a function of time are presented in Fig. 1. The drug levels which peaked (93 ± 4 μg/ml) at 1 min decreased rapidly to $32 \pm 0{\cdot}5$ μg/ml at 10 min. Thereafter, 2-PAM levels fell gradually and only traces ($0{\cdot}6 \pm 0{\cdot}2$ μg/ml) were detected at 480 min of dosing. The data on observed plasma levels of 2-PAM were best fitted to a two-compartment open model and were adequately described by an equation; $Cp = Ae^{-\alpha t} + Be^{-\beta t}$ where Cp was the plasma drug concentration at time t, Ae and Be were intercept terms, and α and β were the overall distribution and elimination rate constants, respectively.

The values for pharmacokinetic parameters which describe distribution and elimination of 2-PAM in buffalo calves are given in Table I. The distribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) of 2-PAM were $0{\cdot}086 \pm 0{\cdot}001$ and $2{\cdot}36 \pm 0{\cdot}09$ h, respectively, whereas the values of apparent volume of distribution ($V_{d(area)}$) and total body clearance (Cl_B) were $1 \pm 0{\cdot}05$ l/kg and 296 ± 13 ml/h/kg, respectively. The half-life of 2-PAM has been reported as 88 min in female rats and 124 min in male rats (Das Gupta *et al.*, 1979). As compared to buffaloes, a shorter elimination half-life of 2-PAM (56–76 min) has been reported in man (Jager *et al.*, 1958; Sidell & Groff, 1971; Swartz & Sidell, 1974). Thus for the maintenance of therapeutic effect, repeated administration of 2-PAM at intervals of 1 h has been recommended in man (Sidell & Groff, 1971). The minimum therapeutic levels of pralidoxime have been established and plasma concentrations over 4 μg/ml were needed for any therapeutic effect (Sundwall, 1961). In the present study, plasma drug levels $\geqslant 4$ μg/ml persisted for 3 h. The results suggest that in comparison to man, 2-PAM may be repeated at less frequent time intervals in buffalo species.

2-PAM significantly ($P < 0{\cdot}01$) increased serum carboxylesterase activity and lowered the serum levels of aspartate aminotransferase, alanine aminotransferase, acid phosphatase, alkaline phosphatase and lactate dehydrogenase enzyme (Table II). On the contrary, organophosphorus insecticides are known to inactivate carboxylesterase and elevate the serum levels of aminotransferases, phosphatases and lactate dehydrogenase in

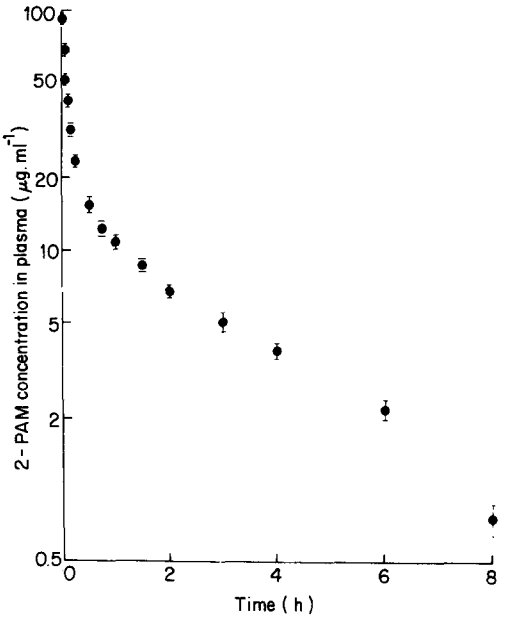

Fig. 1. Plasma concentrations profile of 2-PAM after a single intravenous dose of 15 mg/kg to buffalo calves. Values are presented as mean ± SE of four animals

Table I
Pharmacokinetic disposition of pralidoxime in male buffalo calves after single intravenous administration (15 mg/kg)

Parameter[a]	*Unit*	*Mean*±*SE*[b]
Cp^0	μg/ml	90·9±2·77
A	μg/ml	78·9±3·24
B	μg/ml	12·2±0·76
α	h^{-1}	8·11±0·12
β	h^{-1}	0·296±0·012
$t_{1/2\alpha}$	h	0·086±0·001
$t_{1/2\beta}$	h	2·36±0·09
K_{12}	h^{-1}	5·25±0·05
K_{21}	h^{-1}	1·35±0·08
K_{el}	h^{-1}	1·81±0·13
$V_{d(area)}$	l/kg	1·01±0·05
AUC	μg/ml×h	51·1±2·41
Cl_B	ml/h/kg	296±13·2

[a]Pharmacokinetic parameters have been described by Gibaldi & Perrier (1975).
[b]Values are from four animals.

poisoned animals (Malik & Summer, 1982; Srivastava, Paul & Malik, 1983; Malik, Srivastava & Paul, 1984). The present findings indicate that besides its known ChE reactivating potency, 2-PAM is likely to antagonize other biochemical alterations induced by organophosphates in intoxicated animals.

Table II
Influence of single intravenous administration of pralidoxime (15 mg/kg) on blood enzymes of male buffalo calves

Enzyme	*Time after administration (min)*				
	0	*60*	*120*	*240*	*1440*
Erythrocyte ChE	1978±19	1989±24	1984±21	2023±38	1997±32
Plasma ChE	149±4·2	150±4·5	149±4·4	148±3·9	149±4·4
Serum carboxylesterase	101±2·1	112±1·2[a]	115±1·2[a]	115±2·2[a]	101±1·4
Serum aspartate aminotransferase	57±1·0	51±0·34[a]	48±0·98[a]	47±0·49[a]	56±1·6
Serum alanine aminotransferase	50±1·2	39±0·69[a]	37±1·3[a]	35±0·69[a]	47±1·0
Serum acid phosphatase	4·3±0·11	3·5±0·26	3·4±0·22[a]	3·3±0·10[a]	4·3±0·15
Serum alkaline phosphatase	58±1·3	51±1·1[a]	48±0·47[a]	47±1·1[a]	56±0·66
Serum lactate dehydrogenase	294±7·8	248±9·6[a]	237±8·9[a]	241±6·2[a]	295±7·7

Values given for erythrocyte ChE and plasma ChE (nmol acetylthiocholine hydrolysed/min/ml), serum carboxylesterase (nmol indophenol formed/min/ml), serum aspartate and alanine aminotransferases (nmol pyruvate formed/min/ml), serum acid and alkaline phosphatases (nmol phenol liberated/min/ml) and serum lactate dehydrogenase (nmol pyruvate reduced/min/ml) are mean±SE of the results obtained from four animals.
[a]Statistically significant ($P<0·01$) difference when compared with 0 min value.

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