Research Article

Bioavailability Studies of Paracetamol and Ibuprofen in Single and Combination Dosage in Experimental Rabbits

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ABSTRACT
The main of our work is to study the bioavailability of ibuprofen and paracetamol when given in combination to the rabbits. Single oral dose of 46.0 mg/kg ibuprofen and 56.0 mg/kg of paracetamol were administered separately to two groups of animals and a combination of the same doses was given orally to a III group. Serum level of the drugs in all the three groups were measured spectrophotometrically. The serum peak concentration and rate of elimination of paracetamol is significantly reduced when given with ibuprofen. No such alternation was noticed in serum ibuprofen with paracetamol. Lower elimination rate of paracetamol may increase the effectiveness for a longer time.

Key words: paracetamol, ibuprofen, propylene glycol, bioavailability.

INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory agent and is widely used as such or in combination particularly with paracetamol for treatment of pain with fever. Although the report of individual kinetics of either ibuprofen or paracetamol are available, the effects of combination on kinetics of each are scarcely available in experimental animals like rabbits. In the present study, we have investigated the effect of ibuprofen on absorption and distribution kinetic of paracetamol and vice-versa in rabbits.

MATERIALS AND METHODS

Fifteen healthy New Zealand white rabbits of either sex (2.2 ± 0.12) kg were selected and housed in departmental animal house. They were maintained in standard randomly divided four groups of equal size for the following treatment.

Group-I: A single dose of ibuprofen (46 mg/kg) dissolved in propylene glycol was administered orally.

Group-II: Paracetamol was orally given a single dose of 56 mg/kg in a similar way.

Group-III: A mixture of above doses of both ibuprofen and paracetamol in propylene glycol was administered orally once.

Group-IV: Control group was maintained with a similar volume of vehicle.

Blood samples from four groups of animals were collected after the drug administration in centrifuge tubes from ear vein at 15, 30, 45, 60, 90 and 120 minutes and allowed to clot for separation of serum. Serum sample were first centrifuged and the supernatant of 0.5 ml was mixed with 1 ml of 15% w/v trichloroacetic acid, shaken (thoroughly) for two minutes and centrifuged at 4000 rpm for fifteen minutes. One ml of supernatant solution was taken and diluted to 25 ml with double glass distilled water and the absorbance of the solutions was recorded at 267 nm for ibuprofen and 242 nm for paracetamol with treated serum solution of group IV as blank.

Standard solutions of different concentration of ibuprofen and paracetamol in methanol were prepared separately and standard graphs were made depicting concentration versus absorbance (with methanol as blank) and the respective drug present in the serum samples of group I and group II animals were calculated from the absorbance values using the graphs. While that of serum, ibuprofen and paracetamol of group III animals were calculated following the simultaneous equations method.

Pharmacokinetic analysis of data

The mean values (± SEM) of the serum concentration of drugs mcg.mg^{-1} were plotted against time (minutes) in a semilog graph and other pharmacokinetic parameters calculated and shown in table-1 Student 't' test was applied to find out the significant differences between different groups in respect of drug concentration and serum pharmacokinetic parameters.

RESULTS AND DISCUSSION

Serum concentration (mcg/ml) with time (minutes) in absorption and elimination phases of ibuprofen given alone and in combination with paracetamol have been show in fig-1. In both the cases, the concentration of ibuprofen increased with time and attained the peak at 45 minutes and then declined. In combination therapy with paracetamol, the bioavailability was lower throughout the absorption phase. In the disposition phase, there is no such change. Slight increase of peak concentration of serum ibuprofen at 45 minutes is not significant, compared to that when given alone.

Serum concentration (mcg/ml) with time (minutes) of absorption and elimination phase of paracetamol given alone and in combination with ibuprofen have been show in fig 2. The concentration increased and the peaks attained at 45 minutes and then both declined but in combination therapy with ibuprofen, the bioavailability of paracetamol was lower upto 45 minutes and the rate of disposition was also lower upto 80 minutes compared to single therapy.

The peak serum concentration of paracetamol in combination is significantly higher ($p<0.01$) compared to that given alone.

The lower peak of both the drugs in combination therapy might be because of greater equilibrium distribution along with substantial lower concentration in the central compartment which led to lower AUC values of the drug given in combination.

Table 1: Pharmacokinetics of paracetamol and ibuprofen when given single doses alone and in combination (values are mean ± SEM of 6 replicates)

parameter	unit	Paracetamol		Ibuprofen	
		Alone (1a)	Combination (1b)	Alone (2a)	Combination (2b)
c^s_o	µg.ml^{-1}	2765.47±173.12	7963.02±569.64	3157.53±144.33	7896.57±594.1
k_a	hr^{-1}	0.0673±0.001	0.0561±0.001	0.0693±0.001	0.0570±0.001
β	hr^{-1}	0.0314±0.002	0.0491±0.001	0.0305±0.0003	0.0509±0.001
$t_{1/2}k_a$	hr	10.3±0.1	12.38±0.34	10.01±0.18	12.19±0.32
$t_{1/2}β$	hr	22.38±1.23	14.16±0.46	22.69±0.28	13.16±0.44
Vd_{area}	Lt.kg^{-1}	0.179±0.008	0.226±0.012	0.0955±0.012	0.2494±0.034
AUC	mg.hr^{-1}.Lt^{-1}	10351.11±1016.72	5139.86±338.72	12643.3±797.66	4075.95±649.83
cl_B	Lt.kg^{-1}.hr^{-1}	0.0057±0.0006	0.0111±0.0008	0.0029±0.0003	0.01297±0.002

P< .01when compared to 1(a) and 2(b)
C_s^o =zero time serum concentration.
K_a =Distribution rate constant.
β =Elimination rate constant.
$t_{1/2}k_a$=Biological half-life (distribution phase)
$t_{1/2}β$ = biological half –life (elimination phase)
Vd_{area} =Apparent volume of drug distribution.
AUC= Area under curve.
Cl_B= Total body clearance of the drug.

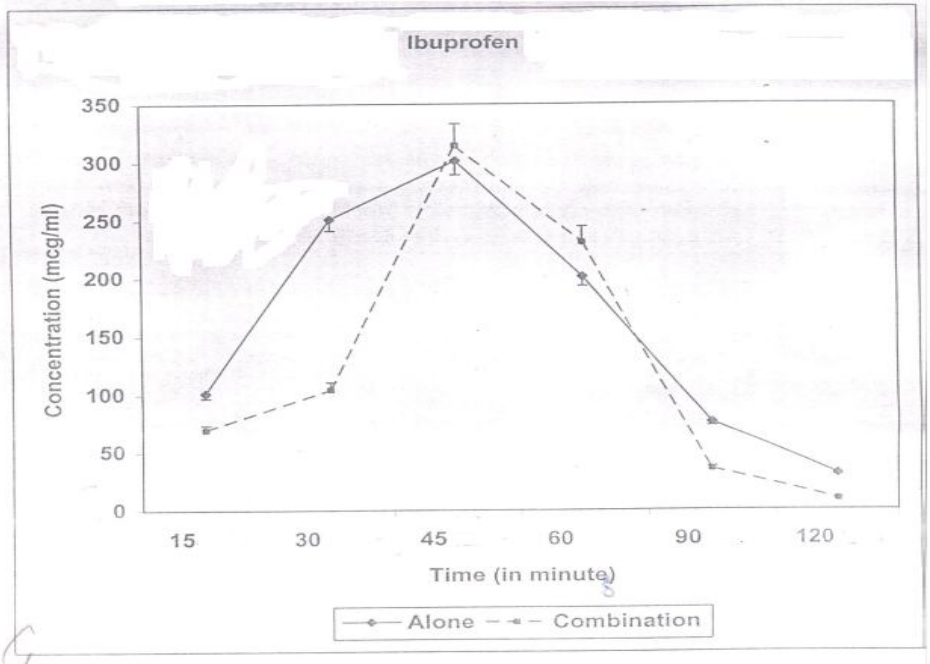

Fig. 1 : Mean Serum concentration of IB against time after a single oral dose (46 mg.kg^{-1}) alone and in combination with PA (56 mg.kg^{-1}).

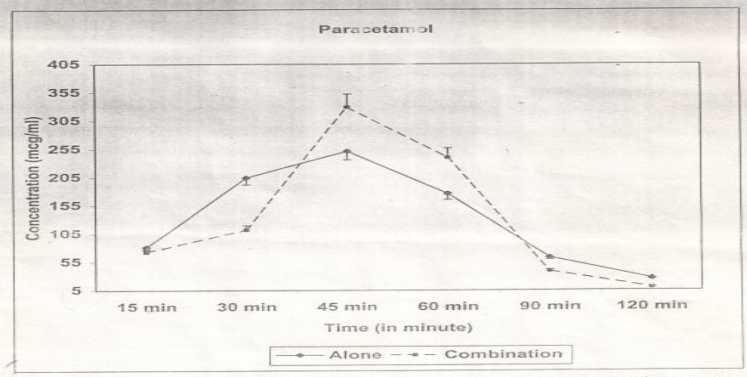

Fig. 2 : Mean serum concentration of PA against time after a single oral dose of (56 mg.kg^{-1}) alone and in combination with IB (46 mg.kg^{-1})

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