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FORMULATION, PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION OF FAST RELEASING COMPRESSED PROPRANOLOL. HCl SUPPOSITORIES

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ABSTRACT

Fast releasing compressed propranolol HCl suppositories were developed and evaluated for their pharmacokinetic and pharmacodynamic performances and compared the results with those obtained after oral administration of a commercial tablet in rabbits. Two disintegrants, microcrystalline cellulose and primogel had significantly influenced the *in vitro* drug release from suppositories without affecting the *in vivo* profiles. The differences in various pharmacokinetic parameters were significant ($p < 0.01$) for oral and rectal administration and were insignificant ($p > 0.05$) among the three suppository formulations evaluated. Drug was rapidly absorbed from the suppositories with more than 3 fold increase in bioavailability following rectal administration. C_{max} of about 140 ng/ml and 49 ng/ml was observed after rectal and oral administrations with the corresponding ß-blockade of more than 95% and about 58% respectively. A relationship for log plasma concentration Vs%ß-blockade was established for orally and rectally administered propranolol HCl.

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INTRODUCTION

Oral administration of propranolol, a widely used ß-blocker is subject to extensive and variable first pass metabolism with a reported systemic bioavailability of about 15-23%[1-3]. Rectal administration of this drug has been reported to improve the bioavailability[4]. In the present study, fast releasing compressed propranolol HCl suppositories particularly suitable to tropical climates have been developed and evaluated for their pharmacokinetic and pharmacodynamic performances and the results were compared with those of a commercial tablet in rabbits. In addition, the effect of disintegrants, microcrystalline cellulose and primogel in different concentrations on in vitro release and bioavailability from the suppositories has been evaluated. Pharmacokinetic and pharmacodynamic relationship for orally and rectally administered propranolol HCl was also investigated.

MATERIALS AND METHODS

Materials

Propranolol HCl I.P. was a kind gift from T.T.K. Pharma, Madras, India. Isoprenaline (Sigma Chemicals, U.S.A.), primogel, microcrystalline cellulose (MCC), polyethylene glycol 4000 (PEG 4000) used were of pharmaceutical grade and all the reagents used were of analytical grade and obtained commercially. Ciplar tablets (propranolol 10 mg/tab) manufactured by Cipla Ltd, Bombay, India were used for oral administration.

Formulation of suppositories

Propranolol HCl was uniformly dispersed (10 mg per suppository) in molten mass of PEG 4000 and slowly cooled down with continuous stirring to effect solidification. The mass was pulverised and passed through 20 mesh screen. Primogel or MCC was added as disintegrant in different concentrations (5, 10 and 15%) separately, thus each formulation contains only one disintegrant at one concentration and mixed thoroughly. Magnesium stearate and talc (1% each) were added and the

granules were compressed into 0.8 g suppositories using fly press. In all, there were seven formulations, three with MCC (5,10 and 15%), three with primogel (5,10 and 15%) and one with no disintegrant.

In vitro release studies

In vitro drug release from compressed suppositories was assessed using dialysis tubing method. A test suppository was placed in a dialysis bag of 5 cm length pretreated with boiling water for 5 min and then with distilled water. The bag was immersed in 300 ml of 1/15 M phosphate buffer, pH 7.4 maintained at 37°C in U.S.P. XX dissolution apparatus. Paddle was rotated at 100 rpm without disturbing the dialysis bag. 2 ml samples were withdrawn at different time intervals and the dissolved drug was estimated spectrophotometrically at 290 nm.

Pharmacokinetic and pharmacodynamic studies

Suppositories with no disintegrant, 5% MCC and 10% primogel and Ciplar tablets each containing 10 mg propranolol HCl were administered to 6 male New Zealand white rabbits (2.0 - 2.5 kg) in a random crossover sequence with a washout period of one week between treatments. Animals were fasted for 24 hrs prior to experiments. Following urethane anaesthesia, (1 g/kg, I.V.) normal electrocardiograms (ECGs) were recorded for all the animals (with Cardioline eta 150 cardiograph Ugobasile, Italy) and the heart rate was computed from the recorded ECGs in all the experiments. To quantify the pharmacodynamic response (ß-blockade), per se isoprenaline induced tachycardia was assessed initially by administering 1 µg/kg in normal saline I.V. into the marginal ear vein over a period of 30 sec and then recording the rise in heart rate. Tablet was administered orally along with 5-10 ml of water and suppositories were inserted into the rectum, 3 to 4 cm from the anus and the anus was closed with a plastic clip to prevent any leakage. About 1.5 ml of blood was collected at 0, 0.5, 1, 2, 3, 4, 6 and 8 hrs from the orbital

sinus into heparinised tubes and the plasma was separated immediately and frozen at -20°C until analysed. Heart rate was recorded after 1, 2 & 6 hrs of administration and to quantify the ß-blockade at the corresponding plasma concentrations, isoprenaline response was recorded as before. Each animal was used as its own control and the % ß-blockade was calculated by taking the difference in the response of isoprenaline per se and in the presence of propranolol. Plasma propranolol levels were estimated spectrofluorometrically by the method of Offerhaus and Van Der Vecht[5], chloroform was used instead of hexane and iso amyl alcohol mixture to improve the extraction efficiency.

Pharmacokinetic and pharmacodynamic analyses

Peak plasma concentrations (C_{max}) and the time of their occurance (t_{max}) were read from the observed plasma concentration profiles. The elimination half-life ($t_{½}$), area under the curve (AUC) and clearance (CL) were obtained using a computer program RAMKIN[6] (unpublished work). Statistical significance of the differences observed in the data was evaluated using ANOVA and Bonferroni's inequality test. A relationship for log plasma concentration Vs %ß-blockade for orally and rectally administered propranolol HCl was examined.

RESULTS

The in vitro release profiles of propranolol HCl from various suppository formulations are shown in Fig.1 (A&B). Release rates were significantly different from suppositories containing 5% MCC, 10% primogel and no disintegrant. Drug release from suppositories containing 5% MCC and 10% primogel was faster among the MCC and primogel containing suppositories respectively. Propranolol plasma concentration time profiles after oral and rectal administration are shown in Fig.2. C_{max}, t_{max}, AUC, $t_{½}$ and CL of propranolol were significantly ($p < 0.01$) affected following rectal administration showing about 3 times and more than 3 times increase in C_{max} and AUC respectively as

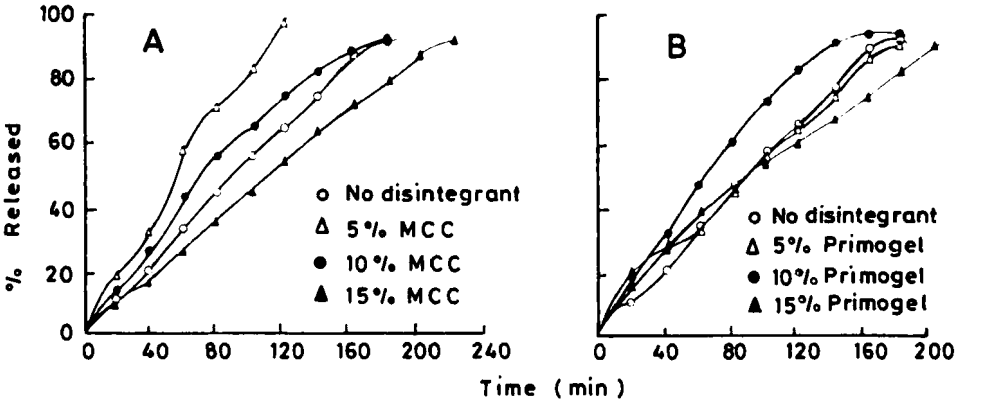

Figure 1 In-vitro release profiles - Effect of MCC (A) and Effect of primogel (B) on the release of propranolol HCl from compressed suppositories.

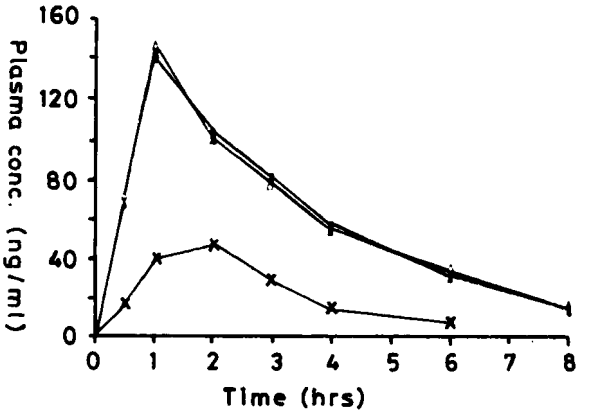

Figure 2 Plasma concentration - time profiles of propranolol after oral and rectal administration (n=6). Oral tablet (x), suppository with : no disintegrant (•), 5% MCC (Δ) and 10% primogel (▲). S.D bars were omitted for the sake of clarity.

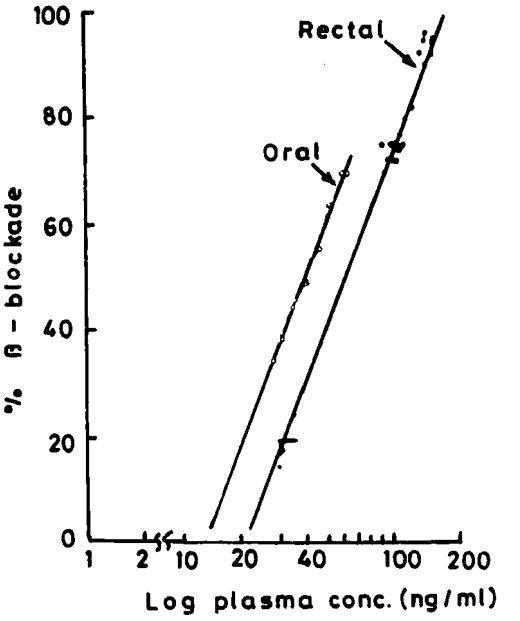

Figure 3 Log plasma concentration Vs % ß-blockade relationship for orally (o) and rectally (•) administered propranolol HCl.

compared to oral administration. The differences in various pharmacokinetic parameters among the three suppository formulations evaluated were insignificant ($p > 0.05$) indicating no effect of disintegrants. A relationship for log plasma propranolol concentration Vs % ß-blockade for oral and rectal administration is shown in Fig.3. Various pharmacokinetic parameters are given in Table 1. Values in parenthesis represent %ß-blockade corresponding to C_{max}. Results were expressed as mean ± SD, n=6.

Even at 6th hour about 18% ß-blockade was observed after rectal administration from all the suppositories evaluated with no recognisable ß-blockade after oral administration.

Table 1

Parameter	Oral tablet	Rectal Suppository with		
		no disintegrant	5%MCC	10%primogel
t_{max},h	1.8±0.4	1	1	1
C_{max},ng/ml	49.0±8.2 (58.3±9.3)	139.6±3.7 (96.5±2.8)	145.5±6.5 (97.8±3.5)	140.8±2.3 (95.6±3.4)
$t_{½}$,h	1.7±0.1	2.1±0.1	2.2±0.2	2.2±0.1
CL,L/h/kg	30.9±3.2	9.4±0.5	9.4±0.5	9.5±0.5
$AUC_{0-\infty}$ ng.h/ml	163.6±14.9	530.4±15.8	537.3±23.0	521.5±11.4

DISCUSSION

Results of the present study revealed significant differences in various pharmacokinetic parameters obtained after oral and rectal administration with 3 fold and more than 3 fold increase in C_{max} and bioavailability respectively after rectal administration of propranolol HCl indicating a significant reduction in first pass metabolism of the drug. Significant shortening of t_{max}, prolonged $t_{½}$ and 3 fold reduction in clearance of the drug after rectal administration clearly indicate a rapid release, absorption and prolonged residence of the drug from compressed suppositories when compared to oral administration of a tablet. This may be attributed to the ready release and absorption of the drug from PEG base and significant reduction in first pass effect following rectal administration.

The differences in pharmacokinetic and pharmacodynamic parameters were insignificant among the three suppository formulations evaluated and also no *in vitro* - *in vivo* correlation could be observed as the disintegrants used did not affect the *in vivo* profiles while significantly influencing the *in vitro* release of the drug from suppositories implying the inability of the dialysis tubing method to simulate the *in vivo* conditions and its unsuitability for the purpose.

With the same 10 mg of the drug, ß-blockade of more than 95% was observed at C_{max} after rectal administration with only 58.3± 9.3% after oral administration. From the log plasma concentration Vs% ß-blockade relationship, 100%ß-blockade could be observed with a plasma concentration of 165 ng/ml and 110 ng/ml after rectal and oral administrations respectively showing that 1.5 times the plasma levels are required after rectal administration to produce a given ß-blockade after oral administration. It can be explained from the fact that the metabolite 4-hydroxypropranolol which is detected after oral administration but not after other routes of administration, is as potent as propranolol[7], resulting in the observed higher ß-blockade after oral administration. Although the ß-blocking effect of the same plasma concentration of propranolol was greater after oral administration, the overall% ß-blockade was higher after rectal administration at any time. The results of the present study strongly support that the administration of propranolol by rectal route is more effective than oral route.

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REFERENCES

1. Shand, D.G., N. Engl. J. Med.,293, 280 (1982).
2. Cid, E., Mella, F., Luchinni, L., Carcamo, M., Monesterio,J. Biopharm. Drug. Dispos.,7, 559 (1986).
3. Riddell, J.G., Harron, D.W.G., Shanks, R.G. Clin. Pharmacokinetics, 12, 305 (1987).
4. De Boer, A.G., Gubbens-Stibbe, J.M., Breimer, D.D. Pharm.Int., 1, 267 (1982).
5. Offerhaus, L., van Der Vecht, J.R. Br. J. Clin. Pharmacol., 3, 1061 (1976).
6. Krishna, D.R., unpublished work.
7. Paterson, J.W., Conolly, M.E., Dollery, C.T., Hayes, A., Cooper, R.G. Pharmacologia Clinica, 2, 127 (1970).