EFFECTS OF AGE AND SMOKING ON THE PHARMACOKINETICS OF PINDOLOL AND PROPRANOLOL

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1 Pharmacokinetic investigations were carried out in a group of 32 ambulant normal male volunteers in order to determine the effect of age and smoking on steady-state plasma levels of pindolol and propranolol. There were four groups of 8: young non-smokers (YNS), young smokers (YS), old non-smokers (ONS) and old smokers (OS). Each subject received, in a randomized cross-over sequence, 5 mg pindolol and 80 mg propranolol three times daily for 2 days with an interval of at least 14 days between the two treatment periods.

2 Neither age nor smoking was shown to have any influence on the time to reach a peak plasma level after pindolol or propranolol. Age, on the other hand, significantly increased the peak plasma levels and the areas under the plasma concentration time curves, and decreased the elimination rate constants, the differences between the age groups being more pronounced for propranolol than for pindolol. No effect of smoking on these parameters was observed.

3 Differences were found between pindolol and propranolol in respect of time to reach a peak plasma level, peak plasma levels and area under the plasma concentration time curves in the groups ONS and YS when related to the YNS control group. Changes observed (with the exception of the time to reach a peak level) tended to be less for pindolol and were considered to be of little clinical relevance.

Introduction

Pindolol is a potent β -adrenoceptor blocking drug. Its β -adrenoceptor blocking activity in man (Hill & Turner, 1969; Aellig, 1976) is, weight for weight, 20–40 times greater than that of propranolol. Pindolol also possesses a longer duration of action.

In pharmacokinetic studies (Meier, 1977; Gugler *et al.*, 1974) after intravenous and oral administration the elimination half-life of pindolol was found to be about 3.5 h. There was no evidence of accumulation of the drug after 5 mg had been given three times daily for 8 days. In man, pindolol is almost completely absorbed and has, owing to a very low first-pass effect, a high systemic availability (Meier & Nüesch, 1977). Pindolol is poorly metabolized (Riess *et al.*, 1975).

Pindolol is well tolerated. It is used mainly in the treatment of hypertension and angina pectoris. Owing to its long duration of action, it can usually be given once a day to those patients requiring a daily dose of up to about 15 mg (Rosenthal, 1977; Morgan *et al.*, 1972). Larger amounts (up to 30 or even 45 mg) are usually given in divided doses.

The finding of Vestal *et al.* (1979a) that mean steady-state blood concentrations of propranolol

were higher in normal subjects over 35 years of age (compared with those <35 years) and in non-smokers (as opposed to smokers) provided the stimulus to carry out the present study which was planned to determine the effects of age and cigarette smoking on the pharmacokinetics of pindolol and propranolol.

Methods

The investigation was carried out in 32 ambulant normal male volunteers, i.e. 8 in each of the following four categories: young non-smokers (YNS), young smokers (YS), old non-smokers (ONS), and old smokers (OS). The young subjects were aged 20–30 years, and the old subjects were above 60 years. The smokers had consumed more than 10 cigarettes a day for at least 6 months. The non-smokers were supposed never to have smoked or to have stopped smoking for at least 5 years; however, it was discovered afterwards that this last group also included some subjects who smoked 2 or 3 cigarettes a day. The mean ages in the subgroups were 25 (YS), 23 (YNS), 66 (OS) and 68 years (ONS). The mean body

weights were 74 (YS), 76 (YNS), 73 (OS) and 79 kg (ONS).

The doses administered were 5 mg pindolol or 80 mg propranolol three times daily for 2 days. A last (seventh) dose was given in the morning on day 3, after which the blood samples were taken. Each subject received both pindolol and propranolol in a randomized cross-over sequence with an interval of at least 14 days between the two treatment periods.

Subjects with impaired hepatic or renal function were excluded from the study, as were those with disturbance of gastric acid secretion, malabsorption syndrome, AV block, marked bradycardia, overt cardiac failure, bronchial asthma, cor pulmonale, peripheral vascular disease or metabolic acidosis.

Each dose was taken along with *circa* 50 ml water and, apart from a ban on alcohol, there were no restrictions placed on those taking part in this study. The vital importance of adhering to a rigid 8-hourly dosage schedule was explained to each subject and the actual intake verified as far as possible. Subjects were physically examined and a chest X-ray, an ECG and blood and urine analyses performed before entering the study.

During the course of the study no concomitant medication was taken by any of the participants. The study was performed in accordance with the Declaration of Helsinki.

Blood samples were taken before the first dose on day 1 (control), before the final dose on day 3 and at 0.5, 1, 2, 4, 6, and 8 h after the final dose on day 3. All blood samples were analysed using a fluorimetric method (Pacha, 1969) for unchanged pindolol and a modified high pressure liquid chromatography method with fluorimetric detection for unchanged propranolol (Mackinchan *et al.*, 1980; Nation *et al.*, 1978).

Analysis of data

The area under the plasma concentration time curves (AUC) in the period 0–8 h on day 3 were individually calculated for each treatment and each subject using the trapezoidal rule. The maximal plasma concentration ($C_p(t_{max})$) and the time at which it was attained (t_{max}) were also determined from the measured values. In addition the rate constants of elimination (k) were calculated from the two or three last plasma concentrations using log-linear regression. These parameters were then tested statistically (each treatment separately) using 2×2 factorial analysis of variance which considered the factor 'age' with 1 degree of freedom (df), the factor 'smoking' (1 df), and the interaction of both (1 df) in order to determine the influence of these factors. In the group of old smokers only seven subjects were evaluated (one

Figure 1 Mean ($\pm$ s.e. mean) steady-state plasma concentrations (ng/ml) of pindolol after the last (seventh) 5 mg dose (3×5 mg/day for 2 days). ●YS ($n = 8$), ■OS ($n = 7$), ▲YNS ($n = 8$) and ○ONS ($n = 8$)

Figure 2 Mean ($\pm$ s.e.mean) steady-state plasma concentrations (ng/ml) of propranolol after the last (seventh) 80 mg dose (3×80 mg/day for 2 days). ●YS ($n = 8$), ■OS ($n = 7$), ▲YNS ($n = 8$) and ○ONS ($n = 8$).

of the eight having dropped out). For the analysis the mean values of the group were inserted for this subject.

The following additional evaluations had the pur-

pose of determining whether the changes observed in the pharmacokinetic parameters of pindolol and propranolol were of similar or different degrees. Since the pharmacokinetic parameters of pindolol

Figure 3 Mean ($\pm$ s.e.mean) pharmacokinetic parameters related to mean values of YNS (percent). □pindolol, ■propranolol. (*) $P < 0.1$, * $P < 0.05$ and ** $P < 0.01$.

Table 1 Pharmacokinetic parameters of pindolol and propranolol, respectively

	$t_{\max}$ (h)			$C_p(t_{\max})$ (ng/ml)			$AUC(0-8h)$ (ng ml ⁻¹ h)			k (h ⁻¹)		
	YS	OS	YNS	YS	OS	YNS	YS	OS	YNS	YS	OS	YNS
Pindolol	Mean	1.7	1.4	2.3	16.1	28.8	20.0	21.2	63	122	58	101
	± s.e.mean	± 0.2	± 0.3	± 0.4	± 2.3	± 4.4	± 3.4	± 3.6	± 9	± 19	± 8	± 23
	Median	2.0	2.0	1.5	16.8	24.0	19.4	17.6	65	99	59	79
Propranolol	Mean	1.4	1.9	1.7	95.0	140.0	69.6	173.3	388	835	327	974
	± s.e.mean	± 0.2	± 0.4	± 0.4	± 15.5	± 16.9	± 10.6	± 28.5	± 59	± 115	± 49	± 210
	Median	1.5	2.0	2.0	86.1	122.3	75.3	187.5	389	732	357	831
										0.408	0.193	0.461
										± 0.106	± 0.015	± 0.059
										0.345	0.172	0.489
										0.287	0.125	0.214
										± 0.112	± 0.016	± 0.018
										0.198	0.127	0.231
												0.257
												± 0.039
												0.034
												0.128

YS: young smokers, OS: old smokers, YNS: young non-smokers, ONS: old non-smokers

and propranolol are basically different they cannot be directly compared with each other but may be so after being subjected to a normalization process. The group of young non-smokers (YNS) was regarded as the normal group. Each single parameter for pindolol and propranolol was separately evaluated in terms of the percentage of the corresponding mean parameter in the control group. The resulting percent values for each and every parameter were tested using Wilcoxon's test for differences between pairs to detect differences between pindolol and propranolol in each of the three groups YS, OS and ONS.

Results

Side effects such as tiredness, dizziness and agitation, mostly of slight degree, were experienced by 19 subjects and occurred with almost equal frequency with both forms of treatment.

The mean ($\pm$ s.e.mean) steady-state plasma concentration – time curves (ng/ml) for each of the four groups after pindolol and propranolol are illustrated in Figures 1 and 2, respectively. In Table 1 the pharmacokinetic parameters $t_{\max}$, $C_p(t_{\max})$, AUC and k are summarized. The results of the statistical analysis are given in Table 2. Figure 3 illustrates details of the pharmacokinetic parameters for pindolol and propranolol related to the mean values in the YNS group, in percent. The statistical analysis of these values is summarized in Table 3, where the mean percent values ($\pm$ s.e.mean) and the medians are also given.

Neither age nor smoking was shown to have any influence on the time to reach a peak plasma level after pindolol or propranolol. Age, on the other hand, significantly increased the peak plasma levels and the areas under the plasma concentration time curves, and decreased the elimination rate constants, the differences between the age groups being more pronounced for propranolol than for pindolol. No effect of smoking on these parameters was observed. The percent values for pindolol and propranolol, normalized in respect of the YNS group, are shown in Table 3 and reveal the following statistically significant differences. Old non-smokers reached maximum plasma concentrations at 2.3 h in the pindolol group, which is 1.7 times longer (170%) than in young non-smokers (1.4 h), and at 1.9 h in the propranolol group, which is 1.11 times longer (111%) than in YNS (1.7 h) ($P < 0.05$). Old non-smokers reached almost the same $C_p(t_{\max})$ values (106%) in the pindolol group as YNS, whereas in the propranolol group these values were 249% ($P < 0.01$).

Summarizing, there were significant differences between pindolol and propranolol in the groups ONS and YS when considering $t_{\max}$, $C_p(t_{\max})$ and AUC

Table 2 Results of statistical analysis (analysis of variance) of pharmacokinetic parameters of pindolol and propranolol, respectively

Parameters	Source	F	Pindolol			Propranolol		
			P(F)			P(F)		
$t_{\max}$	Age	1.13	0.296	NS	0.79	0.382	NS	
	Smoker	0.79	0.381	NS	0.32	0.578	NS	
	Age $\times$ smoker	3.90	0.058	$P < 0.1$	0.28	0.603	NS	
$C_p(t_{\max})$	Age	4.37	0.046	$P < 0.05$	16.05	0.000	$P < 0.001$	
	Smoker	0.30	0.586	NS	0.05	0.832	NS	
	Age $\times$ smoker	2.96	0.096	$P < 0.1$	2.49	0.125	NS	
AUC (0–8 h)	Age	11.12	0.002	$P < 0.01$	19.93	0.000	$P < 0.001$	
	Smoker	0.68	0.415	NS	0.10	0.751	NS	
	Age $\times$ smoker	0.25	0.620	NS	0.66	0.422	NS	
k	Age	11.86	0.002	$P < 0.01$	4.66	0.040	$P < 0.05$	
	Smoker	0.92	0.345	NS	0.20	0.654	NS	
	Age $\times$ smoker	0.01	0.935	NS	0.88	0.357	NS	

(0–8 h), with propranolol exhibiting the greater divergence from the mean values for these parameters in the YNS control group (see also Figure 3).

In the remaining groups and parameters listed in Table 3 there were no significant differences, but some tendencies were noted ($P < 0.1$) which must be interpreted with caution.

Plasma creatinine values for old subjects were 1.13 ± 0.18 mg/100 ml, for young subjects 1.09 ± 0.22 mg/100 ml, for smokers 1.10 ± 0.16 mg/

100 ml and for non-smokers 1.11 ± 0.15 mg/100 ml. Combined for YS, YNS, OS and ONS the values were 1.09 ± 0.11 , 1.09 ± 0.15 , 1.11 ± 0.20 and 1.14 ± 0.15 mg/100 ml, respectively.

Discussion

As pointed out above, there were some light smokers in the non-smoker groups. This point must obviously

Table 3 Results of statistical analysis of pharmacokinetic parameters (percent values) of pindolol and propranolol, respectively, (Wilcoxon's test)

Parameters ¹⁾		Mean $\pm$ s.e. mean; Median		R-value	
		Pindolol	Propranolol		
$t_{\max}$	: YS ²⁾	121 $\pm$ 15; 143	81 $\pm$ 15; 89	5.0	$P < 0.1$
	OS ²⁾	102 $\pm$ 20; 143	109 $\pm$ 24; 118	12.0	NS
	ONS	170 $\pm$ 27; 143	111 $\pm$ 21; 118	3.0	$P < 0.05$
$C_p(t_{\max})$	: YS ²⁾	81 $\pm$ 12; 84	137 $\pm$ 22; 124	0	$P < 0.01$
	OS ²⁾	144 $\pm$ 22; 120	201 $\pm$ 24; 176	3.0	$P < 0.1$
	ONS	106 $\pm$ 18; 88	249 $\pm$ 41; 269	0	$P < 0.01$
AUC (0–8 h):	YS	108 $\pm$ 16; 111	119 $\pm$ 18; 119	10.0	NS
	OS ²⁾	210 $\pm$ 33; 171	255 $\pm$ 35; 224	2.5	$P < 0.1$
	ONS	175 $\pm$ 39; 137	298 $\pm$ 64; 255	3.0	$P < 0.05$
k	: YS ³⁾	96 $\pm$ 25; 77	134 $\pm$ 52; 93	9.0	NS
	OS ²⁾	42 $\pm$ 3; 37	58 $\pm$ 7; 59	3.0	$P < 0.1$
	ONS ⁴⁾	54 $\pm$ 10; 51	70 $\pm$ 18; 59	11.0	NS

YS young-smokers, OS old smokers, YNS young non-smokers, ONS old non-smokers

¹⁾Parameters related to mean values of YNS (percent)

²⁾Without subject no. 8 ($n = 7$)

³⁾Without subject no. 1 ($n = 7$)

⁴⁾Without subject no. 3 ($n = 7$)

be considered when attempting any further interpretation of the results from this study.

Futhermore, it is well known that not only enzyme induction, which can be caused by smoking, but also liver blood flow play a role in the maximal plasma concentrations achieved after oral administration of a drug extracted by the liver. Vestal *et al.* (1979b) have demonstrated a decreased liver blood flow in the elderly irrespective of tobacco smoking. This would result in higher plasma concentrations in elderly people, be they smokers or non-smokers, than in younger subjects.

The observed higher plasma concentrations and decreased elimination rate constants of pindolol and propranolol in the elderly subjects, be they smokers or non-smokers, indicate a decreased clearance of these drugs that could be due either to decreased liver blood flow (e.g. as a consequence of lowered cardiac output) or to a deterioration in renal function.

In conclusion neither age nor smoking was shown to have any influence on the time to reach a peak plasma level after pindolol or propranolol. Age, on the other hand, significantly increased the peak plasma levels and the areas under the plasma concentration time curves, and decreased the elimination rate constants, the differences between the age groups being more pronounced for propranolol than for pindolol. No effect of smoking on these parameters was observed.

Differences were found between pindolol and propranolol in respect of time to reach a peak plasma level, peak plasma levels and area under the plasma concentration time curves in the groups ONS and YS when related to the YNS control group. Changes observed (with the exception of the time to reach a peak plasma level) tended to be less for pindolol and were considered to be of little clinical relevance.

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