INDUCTION OF PROPRANOLOL METABOLISM BY RIFAMPICIN

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The effect of rifampicin on the blood concentration-time curve of propranolol at steady-state following oral administration of 120 mg every 8 h was investigated in six normal, young, male subjects. After an initial 2 week dosing period, all individuals additionally received 600 mg rifampicin daily for 3 weeks followed by a 4 week period during which again only the propranolol was given. In four of the subjects the effects of 900 and 1200 mg rifampicin daily was also studied. Changes in disposition were assessed by estimation of propranolol's oral clearance and elimination half-life during the dosage interval. Rifampicin (600 mg/day) caused a large increase in propranolol's oral clearance (35.7 ± 16.3 vs 96.1 ± 26.9 ml min⁻¹ kg⁻¹, mean $\pm$ s.d.), but neither the elimination half-life nor extent of plasma binding were affected. Increasing the daily dosage to 900 and 1200 mg did not cause any additional changes in oral clearance. Four weeks after discontinuing rifampicin, propranolol's oral clearance had essentially returned to its pre-induction level. The oral clearance of propranolol was significantly smaller ($89.5 \pm 14.4\%$) during the dosage interval immediately after administration of the last rifampicin dose than the value measured 24 h later. The findings are consistent with rifampicin causing induction of the drug metabolizing enzymes responsible for propranolol's biotransformation. The marked reduction in the steady-state propranolol blood concentration that results from chronic rifampicin administration would be expected to result in a significant change in clinical effectiveness of the β -adrenoceptor blocker when the two drugs are used concurrently.

Keywords rifampicin propranolol induction

Introduction

Rifampicin is an important agent in the treatment of pulmonary tuberculosis, advanced systemic infections and in meningococcal prophylaxis. It has become increasingly recognized, however, that such therapy may alter a patient's response to other drugs since rifampicin is a potent inducer not only of its own metabolism (Nitti *et al.*, 1972), but also that of a number of clinically important and widely used agents, including oral anticoagulants, oral contraceptives, corticosteroids, digitoxin and methadone (Zilly *et al.*, 1977). Despite the wide spectrum of enzyme-inducing ability, it has been suggested, based on both animal and human studies, that a certain degree of selectivity in induction may be present (Van den Broek *et al.*, 1981). For example, the *N*-demethylation of antipyrine is increased to a much greater extent than other routes of metabolism (Toverud *et al.*, 1981). Also, the degree of induction of antipyrine metabolism is far less than for hexobarbitone (Bennett *et al.*, 1982; Breimer *et al.*, 1977; Miguet *et al.*, 1977; Ohnhaus & Park, 1979; Ohnhaus & Studer, 1983). Recently, rifampicin has been shown to produce a 10 to 150% increase in the oral clearance of the β -adrenergic receptor blocking

agent, metoprolol, in normal subjects (Bennett *et al.*, 1982). Propranolol is also extensively metabolized by hepatic mixed function oxidases and drug interactions affecting these processes may lead to significant changes in its β -adrenergic receptor blocking activity (Feely *et al.*, 1981; Vestal *et al.*, 1979). Accordingly, the effects of rifampicin on propranolol's disposition in normal subjects were examined to determine whether induction occurs and the extent of any such stimulation in metabolism in relationship to the administered dosage of rifampicin.

Methods

The disposition of propranolol following oral administration was determined in six men aged 23 to 29 years weighing 58 to 108 kg. None had a history of serious illness and all were in good health as judged by physical examination, complete blood count, and routine biochemical tests of hepatic and renal function. All of the subjects claimed to be non-smokers and no alcohol or medications were taken for at least 7 days before, and also during, the study period.

Table 1 Steady-state oral blood clearance ($\text{ml min}^{-1} \text{kg}^{-1}$) of propranolol before, during and after rifampicin administration

Subject	Weight (kg)	Control	Rifampicin 600 mg			Rifampicin 900 mg			Rifampicin 1200 mg		
			Induction Day 21	Post-rifampicin Day 1	Post-rifampicin Day 28	Induction Day 21	Post-rifampicin Day 1	Post-rifampicin Day 28	Induction Day 21	Post-rifampicin Day 1	Post-rifampicin Day 28
1	58.0	19.5	96.3	103.8	24.6						
2	65.8	42.8	122.0	129.5	55.0						
3	86.0	21.1	54.0	70.3	35.9	72.8	103.2	29.8	50.1	66.1	22.7
4	80.5	63.9	85.2	88.5	34.6	70.5	100.0	38.6	109.2	119.8	31.3
5	107.5	35.2	91.0	110.3	28.3	82.2	105.2	31.2	83.0	76.3	23.6
6	64.0	32.0	128.1	138.8	39.3	158.0	137.8	32.3	142.0	130.8	29.3
Mean	77.0	35.7	96.1	106.9	36.3	95.9	111.6	33.0	96.1	98.3	26.7
s.d.	18.3	16.3	26.9	25.4	10.6	41.7	17.6	3.9	39.0	31.8	4.2

Propranolol (120 mg) was administered orally every 8 h during the investigation. Following 2 weeks dosing and after an overnight fast, blood samples were obtained by venepuncture immediately before the next dose, and every hour throughout the subsequent dosing interval. Rifampicin (600 mg) was then given orally as a single daily dose for a period of 3 weeks. Blood samples were again obtained during the propranolol dosing interval concurrent with the final dose of rifampicin and subsequent to an overnight fast. No further rifampicin was administered and on the first and 28th days of the washout period, the dosage interval blood samples were again obtained. In four of the six subjects the study was successively repeated by administering 900 mg/day and then 1200 mg/day of rifampicin, obtaining blood samples during the propranolol dosing interval as before, 3 weeks after treatment with rifampicin and 1 day and 4 weeks following discontinuation.

Blood was collected into glass-stoppered heparinized centrifuge tubes and stored at -20°C until assayed. The propranolol blood concentration was determined by a high performance liquid chromatographic method based on fluorimetric detection (Wood *et al.*, 1978); preliminary studies indicated that neither rifampicin nor its metabolites interfered with this assay. The extent of plasma binding of propranolol was determined by equilibrium dialysis with [^3H]-propranolol using plasma separated from the 2 h blood sample (Wood *et al.*, 1979).

Propranolol's oral blood clearance was determined from the ratio of the administered dose to the area under the blood concentration-time curve during the 8 h dosing interval as determined by the trapezoidal rule (Chiou, 1978). Linear regression of the logarithm of the post-3 h blood concentration time data was used to estimate the elimination half-life. The results were statistically analyzed by the Wilcoxon matched-pairs signed ranks test with $P < 0.05$ taken as the minimal level of significance.

Results

Rifampicin, 600 mg daily for 3 weeks, caused a large reduction in the steady-state blood concentrations of propranolol and a highly significant increase ($P < 0.001$) in the oral clearance of the β -adrenoceptor blocker (Table 1). With the exception of Subject 4, the extent of induction varied between about 250 and 500% relative to the initial control value. This effect was not associated with any change in propranolol's post-absorptive, elimination half-life (4.2 ± 1.0 vs 3.7 ± 0.6 h) nor the extent of its plasma binding (86.0 ± 2.0 vs $85.0 \pm 0.3\%$). No relationship appeared to exist between the extent of induction and the initial oral clearance. Increasing the dosage to 900 mg and then 1200 mg daily did not lead to any further consist-

ent change in oral clearance in the four subjects in whom such studies were performed (Table 1). Four weeks after discontinuing rifampicin the propranolol blood concentrations had essentially returned to their pre-induction levels and, again with the exception of Subject 4, the non-induced oral clearance of propranolol remained reasonably constant over the approximately 6 month period of the study. Propranolol's oral clearance was significantly greater (mean $14.4 \pm 18.0\%$) when determined 24 h after the last dose of rifampicin than when the value was estimated immediately following this dose.

Discussion

The almost complete metabolism of propranolol in man (Paterson *et al.*, 1970) involves a number of different oxidative pathways as well as glucuronidation (Schneck *et al.*, 1980). Both of these types of metabolic transformation have been shown to be inducible with a variety of different substrates and inducing agents (Conney, 1967). The present findings of a marked reduction in the oral, steady-state, blood concentrations of propranolol following treatment with the well-established and potent enzyme-inducing agent, rifampicin, strongly suggests this mechanism for the interaction, although reduced gastro-intestinal absorption cannot be excluded. This conclusion is supported by a previous observation that the cytochrome P-450 content of biopsied liver samples and propranolol's oral clearance were threefold higher in three patients concurrently receiving either phenobarbitone or phenytoin compared to patients not exposed to such enzyme inducing agents (Sotaniemi *et al.*, 1979). The reduction in the area under the oral blood concentration-time curve during the dosage interval without any significant shortening of the elimination half-life after rifampicin treatment is consistent with propranolol's relatively high steady-state hepatic extraction (Kornhauser *et al.*, 1978; Wilkinson & Shand, 1975). A similar observation has also been noted for the interaction of methadone, another high clearance drug, with rifampicin (Kreek *et al.*, 1976).

Recently, the chronic administration of phenobarbitone has been shown to stimulate the metabolism of propranolol in the dog (Vu *et al.*, 1983). In addition, such treatment produces a marked reduction in the unbound fraction of the drug in the plasma presumably due to the simultaneous induction of α_1 -acid glycoprotein (Bai & Abramson, 1982); a major binding protein for propranolol (Piafsky *et al.*, 1978) and other basic drugs (Piafsky, 1980). A similar, but less pronounced effect, has also been observed in epileptic patients receiving known enzyme inducing agents (Routledge *et al.*, 1981; Tiula & Neuvonen, 1982). In the present study, 3 weeks of rifampicin

treatment did not alter the extent of plasma binding of propranolol. This indicates that, unlike inducing agents such as phenobarbitone and other antiepileptic drugs, rifampicin has a negligible effect on the synthesis of this acute phase reactant protein in man.

The induction of metabolizing enzymes is both a dose and time related phenomenon (Breckenridge *et al.*, 1973; Herman *et al.*, 1982; Levy, 1982) and comparative studies must take both of these factors into account. In man it appears that even though both interacting drugs have short elimination half-lives, 2-3 weeks of continuous administration of an enzyme-inducer may be required to establish a new steady-state enzyme level (Breckenridge *et al.*, 1973; Herman *et al.*, 1982). It was for this reason that 3 weeks dosing with rifampicin was used even though significant induction had been observed after considerably shorter times (Miguet *et al.*, 1977; Zilly *et al.*, 1975). After this period of treatment, no further increase in the extent of induction was observed (unpublished results). No additional induction was produced either when the rifampicin dose was escalated to 900 mg and then 1200 mg daily, indicating that, at least with respect to propranolol, the enzyme inducing ability of rifampicin is maximal at daily dosages of 600 mg or less.

The extent of induction following 600 mg rifampicin, as reflected by the increase in propranolol's oral clearance, ranged from about fivefold of the uninduced level of metabolizing activity in Subject 1 to about one and one-half fold in Subject 4. It is noteworthy, however, that on the three subsequent occasions on which this latter individual's uninduced oral clearance was determined it was almost 50% lower than the original estimate. Interestingly, it was retrospectively discovered that this patient was an irregular tobacco smoker to the extent of up to 10 cigarettes/day while all of the other volunteers were indeed non-smokers. It is, therefore, possible that the initial clearance estimate represented an already partially induced situation produced by a temporary resumption of smoking. Certainly, the subsequent determinations and those in the remaining subjects indicated a remarkably small intrasubject variability in propranolol's metabolism over a considerable period of time.

Regardless of the precise degree of induction in Subject 4 following 3 weeks of rifampicin pretreatment, it is apparent that the overall stimulation of propranolol's metabolism was much greater than that reported with metoprolol (Bennett *et al.*, 1982). In the latter instance, the same daily dose of rifampicin was administered, but only for 15 days, and this might account for the smaller effect. However, it is more likely that the difference reflects differential responsiveness of the involved drug metabolizing enzymes for the two β -adrenoceptor blockers. Previous studies with rifampicin in man support such selecti-

vity in that the mean systemic clearances of tolbutamide and hexobarbitone are increased 200 and 300%, respectively (Zilly *et al.*, 1975) while the clearance of antipyrine is enhanced some 150 to 200% (Bennett *et al.*, 1982; Miguet *et al.*, 1977; Ohnhaus & Park, 1979; Ohnhaus & Stuber, 1983; Toverud *et al.*, 1981). Moreover, these differential effects are consistent with the multiple forms of cytochrome P-450 and other drug metabolizing enzymes.

Few studies in man have considered the time required for drug metabolizing activity to return to its baseline value after exposure to an enzyme inducing agent. In seven of 12 subjects the oral clearance of metoprolol was still above its initial control values 15 days after discontinuing rifampicin (Bennett *et al.*, 1982; Toverud *et al.*, 1981), whereas with antipyrine individuals still had elevated activities 13–14 days after stopping the inducer. A relatively slow turnover of induced enzyme is also inferred from the finding that warfarin plasma concentrations took some 20 days to return to control values after several weeks administration of quinalbarbitone (Breckenridge *et al.*, 1973). In the present study, the oral clearance values of propranolol were similar to those obtained prior to rifampicin treatment after 28 days discontinuation of the inducer. It would, therefore, appear that

about a 3–4 week washout period is required for the effects of enzyme induction to disappear in man, even when the causative agent is rapidly removed. In those situations where the inducer is slowly removed from the body, as for example with phenobarbitone, this recovery period may be even longer.

In 11 out of 14 cases propranolol's oral clearance was greater 24 h after the final dose of rifampicin than when the value was determined with the two interacting drugs administered together. This could represent an inhibitory action of rifampicin and/or its various metabolites on the biotransformation of propranolol. However, the small magnitude of the effect probably precludes any clinical consequences for propranolol. The β -adrenoceptor blocking activity of propranolol is well-related to its plasma concentration (Cleveland & Shand, 1972; Zacest & Koch-Weser, 1972). The 20–40% lower propranolol blood concentrations following chronic rifampicin administration would, therefore, be expected to result in a significant change in clinical effectiveness of the β -adrenoceptor blocker when the two drugs are used concurrently.

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