Br. J. clin. Pharmac. (1979), **8**, 43–47

PLASMA PROPRANOLOL CONCENTRATIONS AND THE ERYTHROCYTE SEDIMENTATION RATE

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1 The plasma propranolol concentrations after a single oral dose of 40 mg were measured in 25 patients with rheumatoid arthritis and compared with those of 16 patients with Crohn's disease from a previous study. Thirteen healthy volunteers were used as controls.

2 In both diseases some high and some low values occurred. This scatter did not correlate with any symptoms or biochemical or haematological data other than with the erythrocyte sedimentation rate (ESR).

3 Both sets of patients were therefore separated into two groups depending on whether or not their ESRs were above or below 20 mm/1 h. In both diseases the plasma propranolol concentrations of the patients with a raised ESR were significantly higher than the controls as well as those of the low ESR group.

4 In rheumatoid arthritis the plasma propranolol concentrations of the patients with a low ESR did not differ from those of the controls, but in Crohn's disease they remained significantly higher.

5 In one patient with Crohn's disease there was a dramatic rise in propranolol concentrations during an exacerbation (ESR 91 mm/1 h) compared with those during a remission (ESR 20 mm/1 h).

6 A difference in smoking habits did not seem to have been responsible for the difference in plasma propranolol concentrations.

Introduction

The concentrations of plasma propranolol after an oral dose of 40 mg, were found to be raised in patients with Crohn's disease compared with those of healthy volunteers (Schneider, Babb, Bishop, Mitchard, Hoare & Hawkins, 1976). No cause was found, nor was there any correlation of the increased levels with any clinical or biochemical data including serum levels of proteins, creatinine and liver enzymes. Babb, Bishop, Schneider, Hawkins & Hoare (1976) then suggested that raised plasma propranolol concentrations might be associated with an increased erythrocyte sedimentation rate (ESR). This study was undertaken on patients with rheumatoid arthritis because they tend to have raised ESRs but show no evidence of intestinal disease.

Methods

Twenty-five patients suffering from rheumatoid arthritis took part and their results were compared with those from 16 patients with Crohn's disease including those published previously. The patients with rheumatoid arthritis and the patients with Crohn's disease were divided into two groups: those with a higher and those with a lower ESR taking an arbitrary value of 20 mm/1 h as the dividing line. For details of age, sex and drug treatment see Table 1. Thirteen volunteers (eight men and five women from 19–70 years old with a mean age of 39 years) not suffering from any known disease and with normal biochemical and haematological profiles were used as controls. A full biochemical and haematological profile was carried out in every case on the day of the experiment. All drug treatment was stopped on the morning of the test except for an antibiotic being given to one patient. Informed consent was obtained from all volunteers and patients, and the study had received prior approval from our Research Ethical Committee.

Each person took by mouth on an empty stomach a single tablet of 40 mg propranolol (Inderal). Blood samples were taken before and 0.5, 1, 1.5, 2, 4 and 6 h after taking the drug. Details of the method

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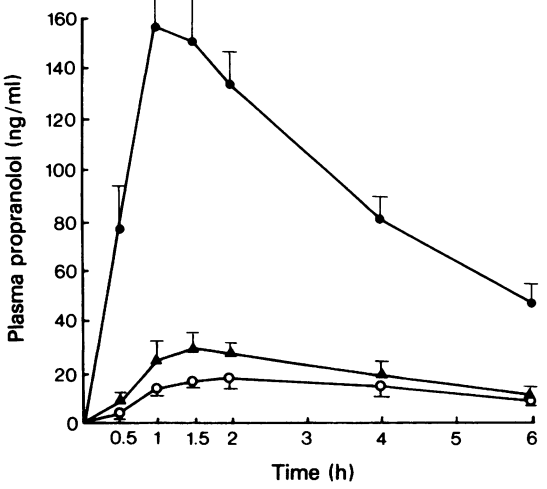

Figure 1 Mean plasma propranolol concentrations (±s.e. mean) in healthy volunteers (○) and in patients with rheumatoid arthritis with ESR ≤20 mm/1h (▲) and with ESR >20 mm/1h (●).

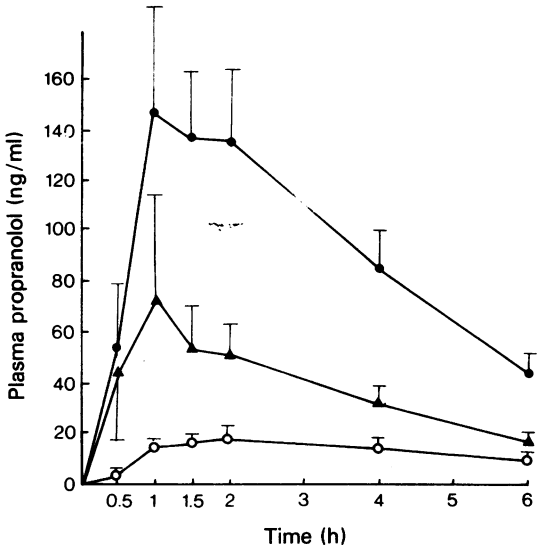

Figure 2 Mean plasma propranolol concentrations (±s.e. mean) in healthy volunteers (○) and in patients with Crohn's disease with ESR ≤20 mm/1h (▲) and with ESR >20 mm/1h (●).

of collecting venous blood were as previously described (Schneider *et al.*, 1976). Assays were done spectrofluorometrically using the method of Shand, Nuckolls & Oates, (1970).

The areas under the plasma propranolol concentration-time curves (AUC) were calculated according to Simpson's rule and the difference between means according to Student's *t*-test.

Results

Figure 1 shows the means of the plasma concentration-time curves from 25 patients with rheumatoid arthritis. The peak value of the group of 16 patients with the higher ESR values was over eight times that of the normal volunteers and the mean concentrations differed significantly at all sampling times (P values for Student's t-test were <0.001). The values of plasma concentrations of the group of 9 patients with rheumatoid arthritis and lower ESR values were almost identical with those of the normal volunteers. The differences between the values of the higher and lower ESR groups were significant at all sampling times (P: 0.05–0.02 at 0.5 h, 0.01-0.001 at 1 h and <0.001 at all other sampling times).

Figure 2 shows the plasma propranolol concentra-

Table 1 Clinical data of the patients with inflammatory diseases

Disease	*ESR (mm/lh)*	*Sex*	*Age (years) Range*	*Mean*	*Numbers of patients receiving drugs*
Rheumatoid arthritis	≤20	4m 5f	31–67	54	Indomethacin 3, Salicylates 2, Sodium aurothiomalate 2 Prednisone (or Prednisolone) 2, Ibuprofen 1, Sulindac 1
Rheumatoid arthritis	>20	6m 10f	39–78	58	Indomethacin 6, Salicylates 5, Sodium aurothiomalate 2, Penicillamine 5, Prednisone (or Predisolone) 2, Ibuprofen 2
Crohn's disease	≤20	6m 3f	26–57	36	Prednisone (or Prednisolone) 7, Sulphasalazine 2
Crohn's disease	>20	4m 3f	22–55	33	Prednisone (or Prednisolone) 5, Sulphasalazine 2, Indomethacin 1, Azathioprine 1

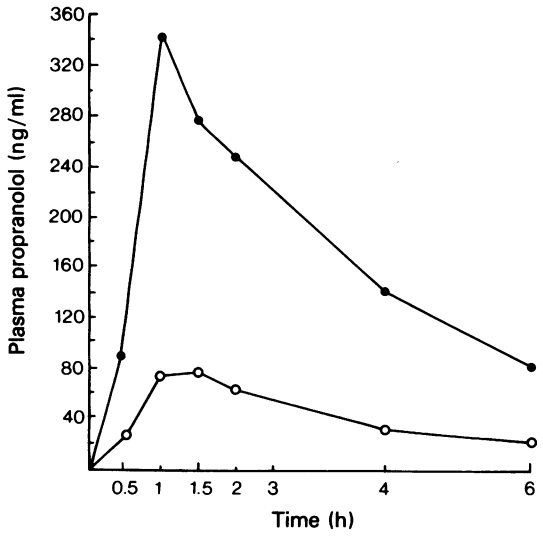

Figure 3 Plasma concentration–time curves of an individual patient suffering from Crohn's disease on two different occasions. Patient C.L.; 14.10.75, ESR, 20 mm/1h (○) (remission); 17.6.76, ESR, 91 mm/1h (●) (exacerbation).

tions of the patients with Crohn's disease. The peak value of the group of 9 patients with ESRs >20 mm/1 h was approximately eight times that of the healthy volunteers, the mean concentrations differing significantly at all sampling times. (P 0.02–0.01 to <0.001). The values from patients with a higher ESR were also significantly greater than those of the group with ESRs ⩽20mm/1 h from 1.5–6 h after administration of the drug. (P 0.02–0.01 to 0.01–0.001). The patients with Crohn's disease with ESRs ⩽20mm/1 h however had plasma propranolol levels significantly higher than the healthy volunteers from 1.5–6 h (P 0.05–0.02 to 0.01–0.001).

Table 2 shows the AUC's truncated at 6 h, and the differences between individual groups. The same relationships were maintained. In both diseases the groups of patients with the higher ESR values had significantly larger AUCs than the healthy volunteers. In the group with ESR ⩽20 mm/1 h the AUCs were significantly smaller than in the higher ESR group, but in the patients with Crohn's disease, still significantly larger than in the healthy volunteers.

Figure 3 shows the two plasma concentration-time curves of an individual patient suffering from Crohn's disease on two different occasions eight months apart. On the first occasion she was in remission with no symptoms and an ESR of 20 mm/1 h. On the second occasion she was in an exacerbation with an ESR of 91 mm/1h. The difference between the two curves is obvious, the peak having risen by a factor of approximately four.

Table 3 shows the difference between the means of

Table 2 Areas under the plasma propranolol concentration-time curves (AUC) in rheumatoid arthritis (Rh A) and Crohn's disease (Cr D) associated with lower and higher ESRs. Differences from healthy volunteers (dHV) and differences between lower and higher ESR groups (dLH)

Disease	*Number of patients*	*ESR (mm/lh)*	*AUC (ng ml^{-1} h) (6h) (mean ± s.e. mean)*	*Student's t-test (P)*	
				dHV	*dLH*
Healthy volunteers controls	13	—	79.19 ± 13.1	—	—
Rh A	9	⩽20	114.3 ± 19.4	NS	<0.001
Rh A	16	>20	570.3 ± 62.1	<0.001	
Cr D	9	⩽20	229.24 ± 68.2	0.05–0.02	0.02–0.01
Cr D	7	>20	544.8 ± 104.8	<0.001	

Table 3 Mean areas under the plasma propranolol–time curves of non-smokers and smokers amongst controls and patients with rheumatoid arthritis or Crohn's disease

	Controls		*Rh A + Cr D ESR↑*		*Rh A ESR↓*		*Cr D ESR ↓*	
	NS	*S*	*NS*	*S*	*NS*	*S*	*NS*	*S*
Number	9	4	14	9	4	5	3	6
Mean AUC (ng ml^{-1} h)	90	55	579.2	563.8	105.6	115.9	365.9	160.9

Rh A, rheumatoid arthritis. Cr D, Crohn's disease. NS, non-smokers. S, smokers.
ESR↑, >20 mm/lh. ESR↓, ⩽20 mm/lh.

the AUCs in non-smokers and smokers in the healthy volunteers and in the patients with rheumatoid arthritis or Crohn's disease. In the controls the mean of the smokers was lower than that of the non-smokers, but in the patients with a raised ESR no such difference was observed. In the patients with a low ESR there was also no difference between non-smokers and smokers in those with rheumatoid arthritis, but in those with Crohn's disease a single very high level amongst the non-smokers had raised the mean to over twice that of the smokers. Recalculation of the difference between the means of the AUCs of the patients with rheumatoid arthritis or Crohn's disease who had a high ESR and the controls using only the non-smokers showed this to have remained highly significant ($P < 0.001$).

Discussion

The results leave no doubt that the raised plasma propranolol concentrations are closely related to the ESR, but no quantitative correlation between either peak propranolol concentrations or the AUCs and the ESR could be established. Subdivision of the two disease groups according to the ESR values ($\leqslant$ or >20 mm/1 h) showed significant differences between the higher ESR groups and the normal volunteers. In the rheumatoid arthritics, the ESR seemed the only factor involved, as propranolol concentrations in the lower ESR group did not differ from those of the controls. This was not so in patients with Crohn's disease which suggested that here another factor was involved. Both diseases are associated with an acute phase inflammatory response, when plasma proteins are markedly altered.

A rise in the level of the plasma orosomucoid as occurs in some inflammatory diseases affects the plasma concentration of free propranolol (Borga, Odar-Cederlöf, Piafsky & Sjöquist, 1977) and a significant negative correlation between the plasma levels of orosomucoid and free propranolol was found by them. In rheumatoid arthritis and Crohn's disease, both of which are frequently associated with raised plasma orosomucoid levels, the mean percentage of the free propranolol was reported as 6.8 and 6.3 respectively compared with a control value of 10.7 (Borga *et al.*, 1977). This implies an increased binding of propranolol to this acute phase reactant and this might interfere with the elimination of propranolol and so account for the increased concentrations found in the plasma, but more work would be required to confirm this.

It has been claimed that smoking increases the metabolism of pentazocine (Vaughan, Beckett & Robbie, 1976) and propranolol (Wood, Vestal, Branch, Wilkinson & Shand, 1978). It therefore seemed possible that a preponderance of smokers in the control groups might have been responsible for the difference between the plasma propranolol concentrations in the different groups in the present investigation. However, omitting the smokers from the group of healthy volunteers did not alter the significance of the difference between the means of the plasma propranolol concentrations of the patients with a raised ESR and the controls, also the means of the smokers and non-smokers in the different groups of patients were almost identical. These findings indicate that the difference between the plasma propranolol concentrations of the patients with a high and those with a low ESR or the controls cannot have been due to differences in smoking habits.

Differences in the rate of gastric emptying might influence peak plasma propranolol concentrations (Castleden, George & Short, 1978), but no relationship was found by them between peak values after the intravenous injection of physiological saline and those obtained after injected metoclopramide or propantheline which respectively stimulate or depress gastric emptying. Propranolol is a weak electrolyte with a pKa of 9.45. According to the theory of non-ionic diffusion (Shanker, Tocco, Brodie & Hogben, 1958), alkaline drugs should be less ionized and therefore better absorbed the more alkaline the medium, and changes in the pH of the microclimate of the luminal surface of the upper jejunum (normal value 5.9) have been suggested as the cause for the raised plasma propranolol levels in Crohn's disease (Cooper, Cooke, Lucas & Blair, 1976). This, however, seems unlikely as the microclimate pH in Crohn's disease with its grossly elevated plasma propranolol levels was found to be only 6.4 whereas in coeliac disease, where the increase in plasma propranolol concentration is marginal only, the rise was considerably greater (pH 7.0) (Lucas, Blair, Cooper & Cooke, 1976).

Propranolol is almost completely metabolized by the liver, so depressed liver function could raise the concentration of propranolol in the plasma. None of these patients showed any symptoms of liver disease and liver function tests carried out on the day of the test were invariably within normal limits.

The phenomenon of raised plasma propranolol concentrations associated with a raised ESR therefore remains unexplained and further experiments with other drugs, other diseases and animal experiments will be required to elucidate it.

We thank the patients who helped us, and also Mrs Janet Babb who carried out the early spectrofluorometric assays and Professor O.L. Wade for his interest and support.

Dr R.N. Allan of the General Hospital, Birmingham, kindly allowed us to include two of his patients with Crohn's disease.

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(Received August 18, 1978)