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Binding to serum α_1-acid glycoprotein and effect of β-adrenoceptor antagonists in rats with inflammation

F.M. Belpaire, M.G. Bogaert, P. Mugabo & M.T. Rosseel

J.F. and C. Heymans Institute of Pharmacology, Gent Medical School, University of Gent, De Pintelaan 185, 9000 Gent, Belgium

1 The β-blocking effect of 4 β-adrenoceptor antagonists with different pharmacokinetic properties was studied after intravenous and intraportal administration to control rats and to rats with experimental inflammation.

2 In rats with inflammation the effects of propranolol and oxprenolol, which are mainly bound to α_1-acid glycoprotein (α_1-AGP), were significantly less after intravenous administration, but not after intraportal administration. In contrast, for metoprolol and atenolol, which are only negligibly serum bound, no difference was observed between control rats and rats with inflammation for either route of administration.

3 Total and unbound serum concentrations of propranolol were measured 20 min after intravenous and intraportal administration.

4 After intravenous administration, in the rats with inflammation total concentrations of propranolol were more than twice, and unbound concentrations less than half those of control rats. After intraportal administration the total concentrations were 8 times, and the unbound concentrations 3 times higher in the rats with inflammation.

5 There was a significant correlation between the β-blocking effect and the unbound concentrations of propranolol after intravenous administration, but not after intraportal administration. The latter finding is probably because the unbound concentrations were supramaximal.

Introduction

Some β-adrenoceptor antagonists are mainly bound to α_1-acid glycoprotein (α_1-AGP) in serum (Belpaire *et al.*, 1982) and the presence of disease or administration of inducing agents can increase the concentration of α_1-AGP and thus serum binding of such drugs (Paxton, 1983). The effect of increased binding on the pharmacokinetics of these drugs has been evaluated in several studies. After oral administration the serum concentrations of propranolol and oxprenolol are higher when inflammation is present, in man (Schneider *et al.*, 1976; 1979; 1981; Kendall *et al.*, 1979) as well as in animals (Belpaire *et al.*, 1981; Bishop *et al.*, 1981; Barber *et al.*, 1983). After intravenous administration, there is still a difference between serum concentrations of the β-adrenoceptor blockers in healthy and diseased individuals, in man (De Leve & Piafsky, 1981; Waller *et al.*, 1982) and experimental animals (Belpaire *et al.*, 1981; Bishop *et al.*, 1981; Barber *et al.*, 1983), but it is less pronounced.

There are few reports about the effects of β-adrenoceptor antagonists in situations where their serum binding is increased. In such situations the β-adrenoceptor blocking effect of propranolol in animals was decreased after intravenous administration, but not after oral administration (Bai & Abramson, 1983; Barber *et al.*, 1983).

Because of the scarcity of data available in the literature, we decided to evaluate whether in the rat with inflammation, the increase in α_1-AGP serum concentration and the increase in binding of some β-adrenoceptor antagonists, influence their β-blocking effect, and whether, for propranolol, this is related to total or unbound drug concentrations in serum. Propranolol and oxprenolol which are bound to α_1-AGP, and atenolol and metoprolol which are not bound to this protein, were injected intravenously and intraportally into healthy rats and into rats with inflammation. Intraportal administration was used to

mimic oral administration in the anaesthetized rat.

Preliminary results have been published elsewhere (Mugabo *et al.*, 1984a,b).

Methods

Preparation of animals

Male Wistar rats weighing from 200 to 450 g were pithed under ether anaesthesia. They were artificially ventilated with air enriched with oxygen, and rectal temperature was maintained at 37°C by a heating pad. Blood pressure was measured from the right carotid artery (Statham P-23AA pressure transducer) and heart rate was measured from an electrocardiogram (ECC transducer); these parameters were registered on a Beckman type R dynograph recorder. The right jugular vein was catheterized for intravenous drug administration; intraportal administration was done by introducing a catheter into a small tributary of the portal vein (catheter used: Clay Adams, PE 20, i.d. 0.38 mm, o.d. 1.09 mm). After pithing the animals, a period of stabilization of 30 min was allowed.

Experiments were done in control rats and in rats in which inflammation was produced by intramuscular injection of turpentine oil (0.5 ml, 24 and 48 h before the experiment) (Jamieson *et al.*, 1972). Erythrocyte sedimentation rate was measured in all animals.

Experimental design

In the first study, isopropylnoradrenaline, dissolved in saline, was infused ($0.01\ \mu g\ kg^{-1}\ min^{-1}$) 3 times for 6 min, at intervals of 14 min. Ten minutes after the last infusion of isopropylnoradrenaline, one of the β-adrenoceptor antagonists, dissolved in distilled water, was infused either intravenously or intraportally over 2 to 3 min according to the weight of the animal. The intravenous and intraportal doses were respectively: for atenolol 0.01 and $0.01\ mg\ kg^{-1}$; for metoprolol 0.03 and $0.12\ mg\ kg^{-1}$; for oxprenolol 0.003 and $0.03\ mg\ kg^{-1}$; for propranolol 0.01 and $0.1\ mg\ kg^{-1}$. Ten minutes after the end of the infusion of the β-adrenoceptor blockers, the same doses of isopropylnoradrenaline were again infused 3 times at intervals of 14 min. The increase in heart rate with isopropylnoradrenaline at different times after the administration of a β-adrenoceptor blocker was expressed as a % of the mean increase in heart rate obtained with the 3 isopropylnoradrenaline infusions before the administration of the antagonist.

In a second study, the β-antagonistic effect of propranolol was measured at the 20th min after intravenous ($0.3\ mg\ kg^{-1}$) or intraportal ($1\ mg\ kg^{-1}$) administration, again by infusion of isopropylnoradrenaline. Immediately after measuring the effect at the 20th min, a blood sample (3 ml) was taken with a Terumo plastic syringe for the determination of serum binding and total serum concentration of propranolol. After clotting for 1 h in a glass tube, the blood was centrifuged and serum stored in glass tubes at −20°C.

Binding experiments

The protein binding of propranolol was measured *in vitro* by equilibrium dialysis for 4 h at 25°C as described previously (Belpaire *et al.*, 1982). Serum (300 μl) was dialysed against an equal volume of phosphate buffer (0.15 M, pH 7.4) containing [^{3}H]-propranolol (sp. act. $20\ Ci\ mmol^{-1}$, $0.47\ \mu Ci\ ml^{-1}$ buffer). Before dialysis, serum was brought to pH 7.4 by addition of 0.1 N HCl (<50 μl per ml serum).

Determination of propranolol concentrations

Propranolol concentrations were measured by h.p.l.c. according to the method of Rosseel & Bogaert (1981) with slight modifications. To 0.25 ml of serum 200 μl NaOH (2.5 N), 30 μl of 0.05 M triethylamine in methylene chloride and 3 ml methylene chloride were added. After shaking and centrifugation the organic layer was evaporated under N_2 at room temperature. The residue was dissolved in 30 μl of the mobile phase and 10 μl injected on the PartiSphere C18 column (Whatman). The mobile phase was a mixture of 85% 0.005 M 1-heptane sulphonic acid in methanol and 15% 0.005 M 1-heptane sulphonic acid in water. Fluorescence detection was carried out with excitation and emission wavelengths at 220 nm and 300 nm respectively.

Statistics

All results are expressed as the mean ± s.e.mean. Statistical evaluation was done with the Mann-Whitney U-test and correlations were calculated by linear regression analysis.

Materials

Atenolol and propranolol hydrochloride were obtained from ICI, U.K.; oxprenolol hydrochloride from Ciba-Geigy, Switzerland and metoprolol tartrate from AB Hassle, Denmark. [^{3}H]-propranolol (sp. act. $20\ Ci\ mmol^{-1}$) was purchased from Amersham, U.K.

Results

The erythrocyte sedimentation rate was increased significantly ($P < 0.001$) in the rats with inflammation (Tables 1 and 2).

The heart rate 30 min after pithing was 240 ± 4

beats min^{-1} ($n = 40$) in control rats, and 245 ± 5 beats min^{-1} ($n = 40$) in rats with inflammation. The increase in heart rate at the end of the isopropylnoradrenaline infusion was 90 ± 5 in the control rats, 81 ± 4 in the rats with inflammation (mean of the 3 administrations).

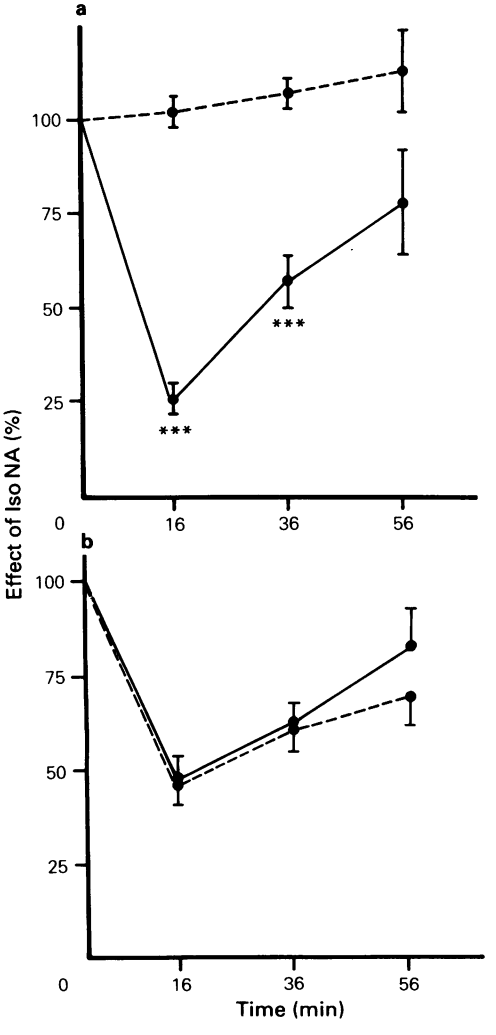

Figure 1 Effect of isopropylnoradrenaline (IsoNA) in control rats (●—●, $n = 5$) and in rats with inflammation (●- - -●, $n = 5$) after (a) intravenous (0.01 mg kg^{-1}) and (b) intraportal (0.1 mg kg^{-1}) administration of propranolol. ***$P < 0.001$, Mann-Whitney U-test. In this and subsequent figures data show mean effect of IsoNA as a % of mean increase in heart rate induced by IsoNA before antagonist administration (see Methods), with vertical lines indicating s.e.mean.

β-Adrenoceptor blocking effect of the different antagonists

Propranolol In the healthy rats, intravenous administration of propranolol (0.01 mg kg^{-1}) decreased the effect of isopropylnoradrenaline to approximately 25%, with a gradual recovery in the following hour, as can be seen in Figure 1a. In the animals with inflammation, no inhibition of the isopropylnoradrenaline effect was seen with the same dose of propranolol given by the same route.

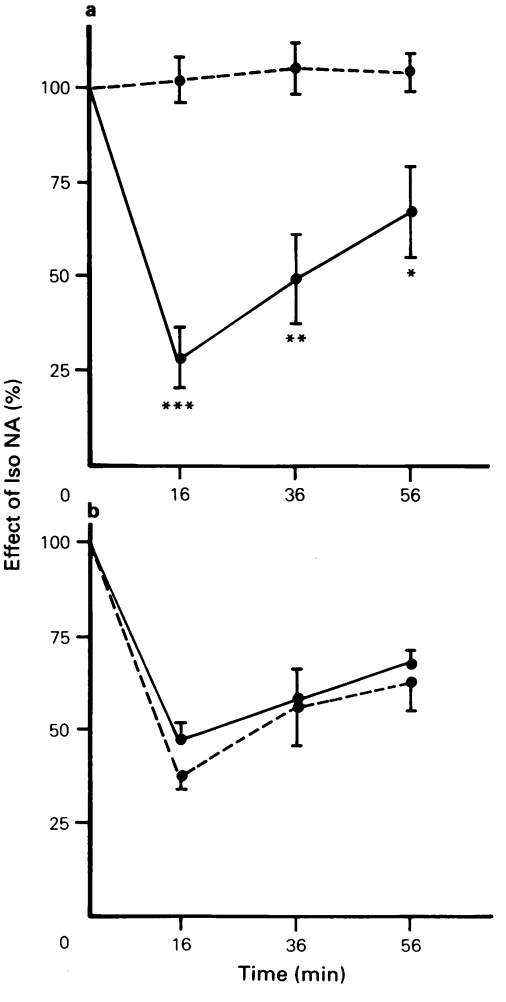

Figure 2 Effect of isopropylnoradrenaline (IsoNA) in control rats (●—●, $n = 5$) and in rats with inflammation (●- - -●, $n = 5$) after (a) intravenous (0.003 mg kg^{-1}) and (b) intraportal (0.03 mg kg^{-1}) administration of oxprenolol. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, Mann-Whitney U-test.

Intraportal administration of a 10 times higher dose of propranolol resulted in a 50% reduction of the isopropylnoradrenaline tachycardia after 16 min in the control animals and in those with inflammation, followed by a gradual recovery (Figure 1b).

Oxprenolol Intravenous administration of oxprenolol (0.003 mg kg^{-1}) induced an effect similar to that seen with propranolol, a reduction of the isopropylnoradrenaline response to about 25% in the control animals and no effect in the animals with inflammation (Figure 2a). After intraportal administration of oxprenolol (0.03 mg kg^{-1}), a reduction of the isopropylnoradrenaline effect to about 50% was seen in both groups of rats (Figure 2b).

Atenolol After intravenous administration of atenolol (0.01 mg kg^{-1}), the isopropylnoradrenaline effect was reduced to approximately 35% in both the control animals and those with inflammation (Figure 3a). After intraportal administration of the same dose of atenolol, a similar reduction of the isopropylnoradrenaline effect was seen, again with no difference being apparent between the control rats and the rats with inflammation (Figure 3b).

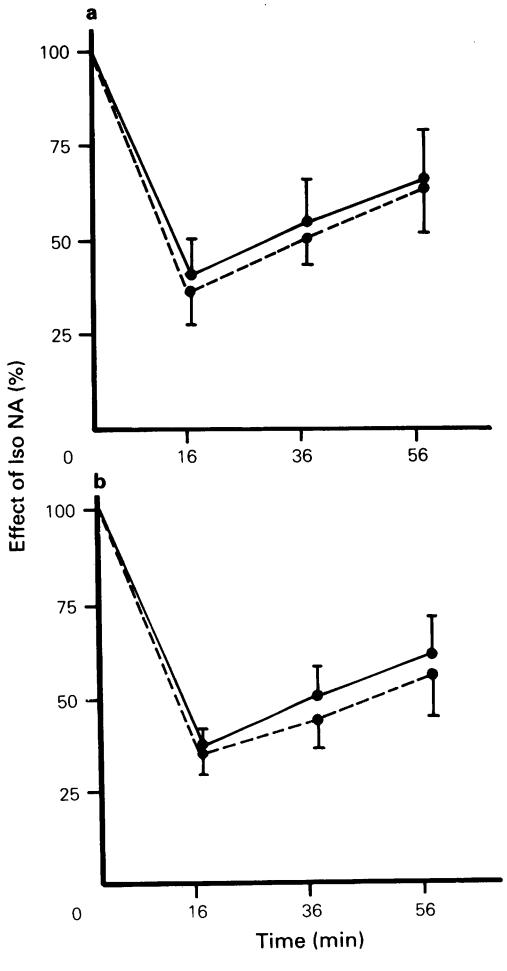

Figure 3 Effect of isopropylnoradrenaline (IsoNA) in control rats (●—●, $n = 5$) and in rats with inflammation (●---●, $n = 5$) after (a) intravenous (0.01 mg kg^{-1}) and (b) intraportal (0.01 mg kg^{-1}) administration of atenolol.

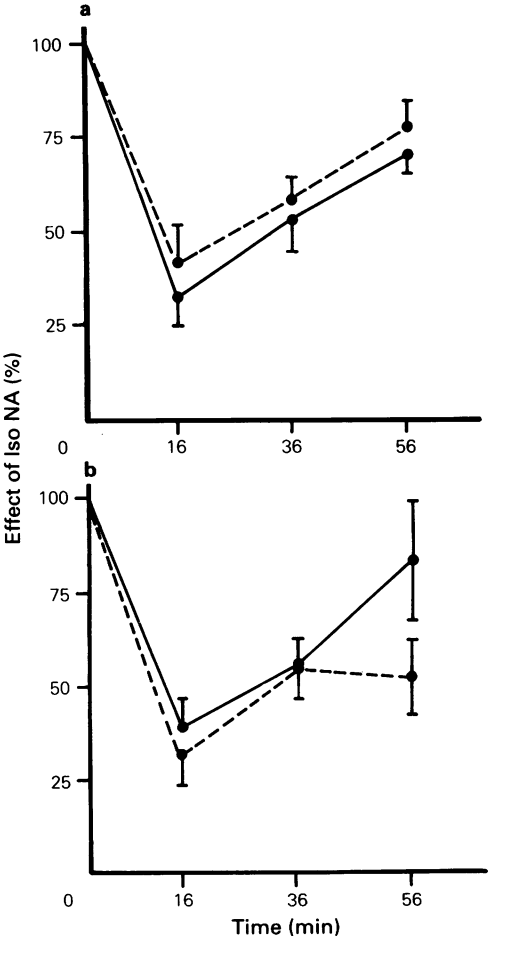

Figure 4 Effect of isopropylnoradrenaline (IsoNA) in control rats (●—●, $n = 5$) and in rats with inflammation (●---●, $n = 5$) after (a) intravenous (0.03 mg kg^{-1}) and (b) intraportal (0.12 mg kg^{-1}) administration of metoprolol.

Metoprolol Intravenous administration of metoprolol (0.03 mg kg^{-1}) reduced the effect of isopropylnoradrenaline to about 30% in control animals, followed by a gradual recovery of the isopropylnoradrenaline effect with time (Figure 4a). The effect in the animals with inflammation was somewhat smaller. A 4 times higher dose of metoprolol given intraportally led to a 40% decrease of the isopropylnoradrenaline-induced tachycardia in control animals. A similar effect was observed in the animals with inflammation (Figure 4b).

The β-adrenoceptor blocking effect of propranolol in relation to its total and unbound concentrations

Intravenous administration Twenty minutes after intravenous administration of propranolol (0.3 mg kg^{-1}), the effect of isopropylnoradrenaline was decreased significantly ($P<0.001$) in control rats to 10%, and in rats with inflammation to 55%. The unbound propranolol fraction was 5 times lower (Figure 5, Table 1) in the rats with inflammation than in the control rats ($P<0.001$), and the total propranolol concentrations were not significantly increased. The calculated unbound concentrations of propranolol were significantly reduced ($P<0.01$) and there was a correlation between the β-blocking effect of propranolol and the log of the unbound concentration of propranolol ($r = 0.687$; $P<0.01$; $n = 12$).

Intraportal administration Twenty minutes after intraportal administration of propranolol (1 mg kg^{-1}) there was an approximately 80% inhibition of the isopropylnoradrenaline effect in both groups of rats

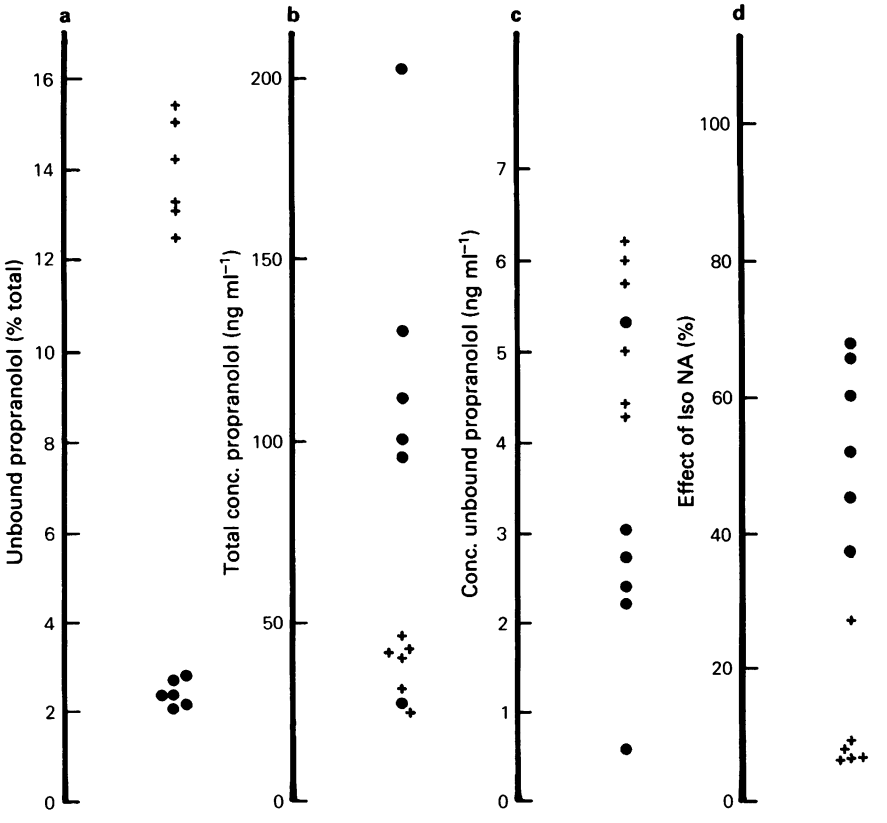

Figure 5 (a) Percentage unbound propranolol, (b) total and (c) unbound propranolol concentrations and (d) isopropylnoradrenaline (IsoNA) effect, in control rats (+) and in rats with inflammation (●), after intravenous administration of propranolol (0.3 mg kg^{-1}).

Table 1 Intravenous administration of propranolol (0.3 mg kg^{-1}) in control rats and in rats with inflammation

Measurement	*Control rats*	*Rats with inflammation*
Sedimentation rate (mm per 1 h)	0.7 ± 0.1	21.4 ± 4.5***
Unbound propranolol (%)	13.9 ± 1.2	2.4 ± 0.3***
Total propranolol concentration (ng ml^{-1})	38 ± 3	112 ± 23
Unbound propranolol concentration (ng ml^{-1})	5.3 ± 0.4	2.7 ± 0.6**
% inhibition of IsoNA-effect	89 ± 3	45 ± 5***

Results shown are means ± s.e.mean ($n = 6$); **$P < 0.01$, ***$P < 0.001$, significantly different from control values (Mann-Whitney U-test). IsoNA = isopropylnoradrenaline.

(Figure 6 and Table 2). The percentage of unbound propranolol in rats with inflammation was significantly lower than that in the control rats ($P < 0.001$). The total serum concentrations were approximately eight times higher in the rats with inflammation. The calculated unbound drug concentrations were significantly higher in rats with inflammation ($P < 0.05$), but they varied widely in both groups. There was no significant correlation between the β-blocking effect of propranolol and its unbound concentration ($r = 0.378$, $n = 12$).

Discussion

This study aimed to evaluate the effect of inflammation and increased binding to α_1-AGP on the kinetics and effects of β-adrenoceptor antagonists.

In the first study the pharmacological effect of four β-adrenoceptor blockers was studied in control rats

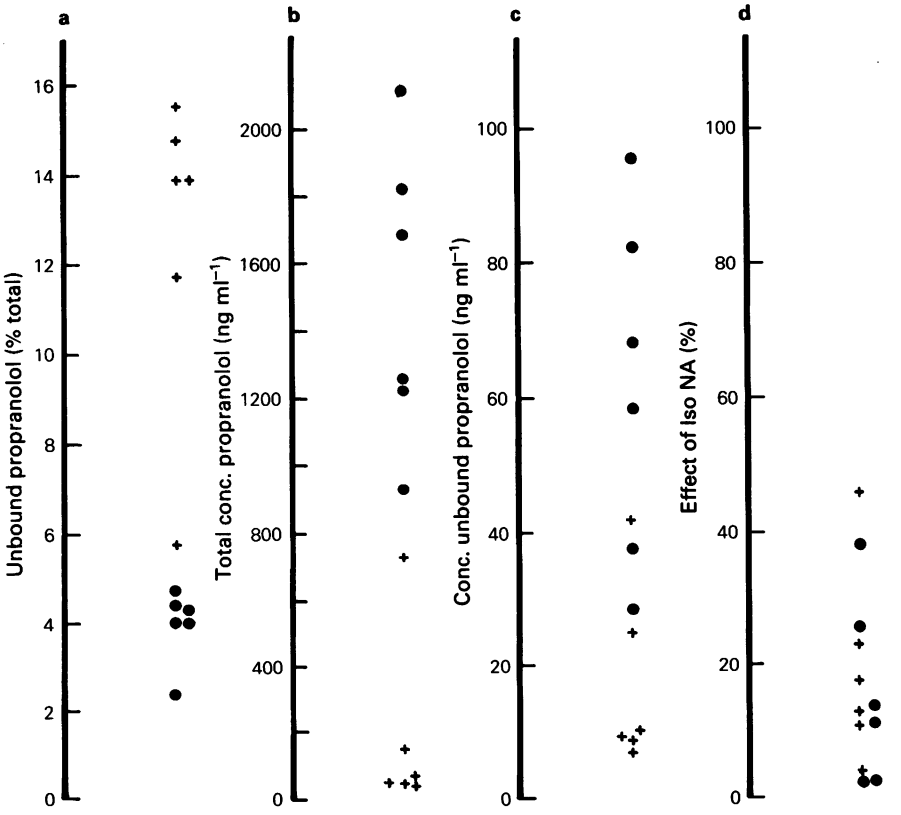

Figure 6 (a) Percentage unbound propranolol, (b) total and (c) unbound propranolol concentrations and (d) isopropylnoradrenaline (IsoNA) effect, in control rats (+) and in rats with inflammation (●), after intraportal administration of propranolol (1 mg kg^{-1}).

Table 2 Intraportal administration of propranolol (1 mg kg^{-1}) in control rats and in rats with inflammation

Measurement	*Control rats*	*Rats with inflammation*
Sedimentation rate (mm per 1 h)	0.9 ± 0.1	19.7 ± 2.1**-**
Unbound propranolol (%)	12.6 ± 1.5	4.0 ± 0.4**-**
Total propranolol concentration (ng ml^{-1})	193 ± 106	1519 ± 186***-
Unbound propranolol concentration (ng ml^{-1})	17.3 ± 5.6	61.9 ± 10.4*-
% inhibition of IsoNA-effect	81 ± 6	84 ± 23

Results shown are means ± s.e.mean ($n = 6$); *$P < 0.01$, ***$P < 0.001$, significantly different from control values (Mann-Whitney U-test). IsoNA = isopropylnoradrenaline.

and rats with inflammation. Propranolol and oxprenolol were chosen because their serum binding increases in inflammation as a consequence of an increased α_1-AGP concentration, while metoprolol and atenolol were studied because they are only negligibly bound to serum proteins (Belpaire *et al.*, 1982). Propranolol, oxprenolol and metoprolol are drugs which are extracted and metabolized by the liver, whereas atenolol is excreted unchanged in the urine.

Intravenous administration of the β-adrenoceptor antagonists

After intravenous administration, the β-blocking effects of propranolol and oxprenolol, which are mainly bound to α_1-AGP, were decreased in rats with inflammation. This has also been found for propranolol after intravenous administration in rats with adjuvant induced arthritis (Barber *et al.*, 1983). The β-blocking effect of atenolol and metoprolol, which are only weakly bound to serum proteins, was not changed by the inflammation. As the unbound concentration of a β-adrenoceptor blocker is thought to be responsible for its pharmacological effect (McDevitt *et al.*, 1976), these results suggest that the increase in serum binding of oxprenolol and propranolol in our rats with inflammation, was responsible for the decrease in pharmacological effect. This was evaluated in a second study.

In the second study the decrease by propranolol of the effect of isopropylnoradrenaline was more pronounced than in the first study, due to the higher dose of the antagonist used. The effect of propranolol in rats with inflammation was, here too, markedly smaller than in control rats. The total concentrations of propranolol after intravenous administration were more than doubled in the rats with inflammation, which is in agreement with results in rats with adjuvant induced arthritis (Bishop *et al.*, 1981; Barber *et al.*, 1983) and in patients with various inflammatory diseases (De Leve & Piafsky 1981; Waller *et al.*, 1982). The unbound propranolol concentrations were, however, lower in our rats with inflammation than in the control rats, and these unbound concentrations correlated well with the β-blocking effect. De Leve & Piafsky (1981) mention a decreased area under the curve for unbound drug, and relatively unaffected total drug concentrations of propranolol in patients with rheumatoid arthritis.

According to the physiological approach to hepatic drug clearance of Wilkinson & Shand (1975) one can expect, for a drug with a high hepatic extraction such as propranolol, that hepatic clearance is not altered by changes in binding, at least if these changes do not exceed certain limits. Therefore, increased binding in itself, while altering the shape of the plasma concentration-time curve, is not expected to change the area under the curve for total drug after intravenous administration. We found higher total concentrations at the 20th min, but this could be due to an altered shape of the curve without a change in the area under the curve. Barber *et al.* (1983) found a higher area under the curve (AUC) for total drug in inflammation, and to explain their results, one has to assume either that hepatic blood flow has decreased, or that the unbound fraction has declined to a degree such that hepatic clearance indeed decreases (Wilkinson & Shand, 1975). For the unbound concentrations, it is expected that increased binding leads to a decrease of the AUC and consequently a decreased pharmacological effect. Such a decreased effect was found in our experiments and also in the study of Barber *et al.* (1983) in rats with adjuvant arthritis.

Intraportal administration of the β-adrenoceptor blockers

After intraportal administration the β-blocking effect of the four drugs as a function of time, was not altered by inflammation. This was also found by Barber *et al.* (1983) for propranolol in rats with adjuvant induced arthritis. This suggests that the unbound concentrations of propranolol and oxprenolol were not changed by inflammation. It should be mentioned that the doses of metoprolol, oxprenolol and propranolol used after intraportal administration had to be much higher than after intravenous administration, due to the important first pass effect.

In the second study, where we measured the β-blocking effect of propranolol, together with its total

and unbound concentrations after intraportal administration, there was, as in the first study, no significant difference in the inhibition of the effect of isopropylnoradrenaline between the control rats and the rats with inflammation. The total propranolol concentrations after intraportal administration were about eight times higher in the rats with inflammation, and this is in agreement with the results in rats with adjuvant induced arthritis (Bishop *et al.*, 1981; Barber *et al.*, 1983) and in patients with inflammatory diseases (Kendall *et al.*, 1979; Schneider *et al.*, 1979; 1981; 1982); the unbound propranolol concentrations were also significantly higher. There was no significant correlation between the percentage inhibition of isopropylnoradrenaline activity and unbound concentration after intraportal administration, which contrasts with the situation after intravenous administration. This could be because we used a supramaximal dose, or due to the presence of an active metabolite, 4-hydroxypropranolol, which can be formed after intraportal administration (Paterson *et al.*, 1970).

Our results after intraportal administration and those in the literature agree with the theoretical predictions which can be made when using a physiological approach to drug clearance. The observation that after oral or intraportal administration the area under the curve for total drug increases much more than after intravenous administration, can be explained by the fact that for high extraction drugs, extraction decreases and bioavailability increases with increased binding. The area under the curve for unbound drug should not change much when binding increases, and consequently the pharmacological effect in the two groups of rats should not be different.

The finding that the effect of intraportal administration of metoprolol, a drug which undergoes substantial first pass extraction and which is not bound to α_1-AGP, is not influenced by inflammation, suggests that there are probably no important changes in intrinsic clearance of the β-adrenoceptor antagonists in this state, although in rats with inflammatory disease the metabolism of some drugs is impaired (Whitehouse & Beck, 1973).

Our results show that the increase in serum binding of the β-adrenoceptor blockers induced by inflammation is accompanied by a higher total drug concentration, lower unbound concentration and a smaller pharmacological effect after intravenous administration. However, after intraportal administration, the total drug concentration is increased considerably and the unbound concentration increased to a lesser extent, but the β-blocking effect remains unchanged when serum binding is increased by inflammation.

Hence, these findings demonstrate that for β-adrenousceptor blockers mainly bound to α_1-AGP, one should consider unbound drug concentrations in the design of dose regimens for use in diseases where the binding of these drugs is altered.

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