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Pharmacological properties of β-adrenoceptor blocking drugs

U. Borchard

β-adrenoceptor blocking drugs are widely used for the treatment of cardiovascular diseases such as arterial hypertension, coronary heart disease and supraventricular and ventricular tachyarrhythmias. They may also be beneficial in the hyperkinetic heart syndrome, hypotensive circulatory disorders, portal hypertension, hyperthyroidism, tremour, migraine, anxiety, psychosomatic disorders or glaucoma. In recent years even patients with heart failure have been successfully treated with β-blockers initially given at very low doses.

A great number of β-adrenoceptor blocking drugs are now available for clinical use which differ widely with respect to their pharmacodynamic and pharmacokinetic properties [1, 2]. They all interact with β-adrenoceptors forming drug receptor complexes so that endogenous norepinephrine and epinephrine are hindered from accessing the receptor. This leads to a competitive antagonism which is characterized by a parallel shift of the concentration-response curve of the agonist to the right. The β-receptor blockade can be completely reversed by high concentrations of the agonist.

The various β-blockers differ with respect to their β-receptor affinity, β_1-selectivity, partial agonist activity and physicochemical properties (lipophility, stereospecificity) which all may be of particular importance for clinical use. In addition, pharmacokinetic properties such as absorption, bioavailability, metabolism, volume of distribution and elimination (hepatic and/or renal clearance) may guide therapy in special patients.

Table 1: Coexistence of β_1- and β_2-receptors in different organs

Organ	Subtype	Function
Presynaptic		
Noradrenergic nerve ending	β_2	Norepinephrine release ↑
Postsynaptic		
Heart	β_1, (β_2)[a]	Sinus rate ↑ Contractility ↑ AV-conduction ↑
Gastrointestinal tract	β_1	Muscular tone ↓
Kidney	β_1, (β_2)[a]	Renin release ↑
Fat cells	β_1, (β_2)[a]	Lipolysis ↑
Bronchi	β_2	Muscular tone ↓
Blood vessels	β_2, (β_1)[b]	Muscular tone ↓
Uterus	β_2	Muscular tone ↓
Pankreas (β-cells)	β_2, (β_1)[a]	Insulin release ↑
Thyroid gland	β_2, (β_1)[a]	$T_4 \rightarrow T_3$ conversion ↑
Incretory glands	β_2, (β_1)[a]	Secretion of parathormone ↑ calcitonin, glucagon ↓

[a] receptor subtype coexistence (eg, in the heart 20 % β_2)
[b] human cerebral blood vessels

Pharmacodynamic properties

In many organs there is a coexistence of β_1- and β_2-receptors (Table 1). For example, in the normal human heart about 80% of the β-receptors are of the β_1-subtype. In heart failure β_1-receptors are down-regulated so that a relatively higher proportion of β_2-receptors can be measured [3]. The physiological and therapeutic actions of a β-blocker depend on the actual density of β_1- and/or β_2-receptors in the different organs, on the affinity of the β-blocker and on the local drug concentration.

Affinity

β-blockers with high affinity for β-adrenoceptors (Table 2) are effective in small doses if their bioavailability is not too low [4, 5]. Their action still continues even if they are washed out of the extracellular space. Consequently their duration of action cannot be predicted by the plasma half life of the β-phase of elimination [3]. This holds true for many drugs with high affinity and short plasma half life (2–4 h for the β-phase). Penbutolol, for example, has a high affinity, dissociates slowly from the β-receptor, the $t_{1/2}$ value (β-phase) is about 2 h, the terminal half life is about 27 h and the duration of action after a 40 mg dose amounts to about 48 h.

Table 2: Pharmacodynamic properties of ß-blockers

	Affinity (pA_2-values)							
	Chrono-tropy	Inotropy	Trachea	β_1-Sel.	Sel.-Index	PAA	PC	UMA
Acebutolol	7.3	7.0	6.4	+	0.9	+	0.17	(+)
Alprenolol	8.6	8.6	8.4	–		+	3.3	+
Atenolol	7.6	7.4	5.9	+	1.7	–	0.0033	–
Betaxolol	8.6	8.6	6.2	+	2.4	–	3.9[1])	(+)
Bisoprolol	8.8	8.9	6.4	+	2.4	–	3.0	+
Bopindolol	9.51[2])	9.37[2])	9.65[2])	–		(+)		
Bupranolol	8.7	9.0	9.5	–		–	0.38	+
Carazolol	9.9	9.8	9.4	–		–	13.7	+
Carteolol[4])	9.2	9.0	9.3	–		+	0.214	(+)
Carvedilol[4])	9.1		8.87	–		–	226[1])	+
Celiprolol	7.6	8.1	6.8	+	0.8	+	0.152	(+)
Esmolol[5])	6.9	6.9	5.3	+	1.6	–		–
Mepindolol	9.9	9.5	9.0	–		+	0.54	(+)
Metipranolol	9.9	9.5	9.0	–		+	0.214	(+)
Metoprolol	7.5	7.7	6.4	+	1.1	–	0.18	(+)
Nadolol	7.9	7.2	7.5	–		–	0.008	–
Nebivolol[4])	8.24		5.77	+	2.47	–		+
Oxprenolol	8.5	8.7	8.5	–		+	0.51	(+)
Penbutolol[3])	8.6	8.9	9.0	–		(+)	50.0[1])	+
Pindolol	9.2	9.4	9.0	–		+	0.20	(+)
Propranolol	8.4	8.5	8.5	–		–	5.4	+
Sotalol	6.1	5.9	5.9	–		–	0.011	–
Talinolol	7.0	7.0	5.33	+	1.7	–		–
Tertatolol[4])	9.37		8.83	–		–	2.5[1])	+
Timolol[3])	8.7	8.7	8.2	–		–	0.28	(+)

Sel.-index = selectivity index: pA_2 chronotropy minus pA_2 trachea; PAA = partial agonist activity; PC = partition coefficent n-octanol/phosphate buffer (temperature 20–30 °C. pH 7.0; [1]) pH 7.4); UMA = unspecific membrane action; [2]) active metabolite; [3]) S-isomers; [4]) vasodilative; [5]) only *i.v.*-application

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β_1-selectivity

Most of the therapeutic actions of β-blockers are due to inhibition of β_1-receptors whereas a great number of specific side-effects are brought about by inhibition of β_2-receptors.

In most therapeutic situations β_1-selective drugs are as effective as non-selective drugs. However, β_1-selective agents are better tolerated than non-selective β-blockers as they have fewer side effects [6].

Experiments on isolated heart preparations (chronotropy: β_1) and tracheal strips (bronchodilatation: β_2) as well as binding experiments with radio-labeled β-blockers have shown the following sequence of β_1-selectivity: bisoprolol ~ betaxolol ~ nebivolol > atenolol ~ talinolol > metoprolol > acebutolol ~ celiprolol (Table 2). One major advantage of a high β_1-selectivity is the lower incidence of air-way obstruction (β_2-receptor blockade) and the bronchodilatory action of β_2-agonists even in the presence of a β_1-selective blocker. However, in patients with bronchial asthma all β-blockers are contraindicated independent of their β_1-selectivity. It is a further advantage of β_1-selective drugs that they show only minor effects on glucose and lipid metabolism. The benefits of a high β_1-selectivity of a β-blocker in clinical practice are summarised in Table 3.

Partial agonist activity

The partial agonist activity (PPA) or intrinsic sympathomimetic activity (ISA) of some β-blockers (Table 2) is due to the similarity of the molecules of the agonist and antagonist. Binding of β-blockers with ISA to the receptor induces a weak signal transduction but at the same time antagonises the action of β-agonists. Maximal ISA of β-blockers needs full receptor occupation and does not reach the maximal effect of a full agonist so that ISA of β-blockers is called partial agonist activity. β-blockers with ISA might be useful in patients with low heart rate [7] or with low HDL-cholesterol and/or high triglycerides [2]. However, clinical studies have shown that β-blockers with ISA are less effective in reducing mortality in patients with acute myocardial infarction [8]. In summary, the clinical significance of ISA has to be regarded as low.

Physico-chemical properties

Lipophilicity

β-blockers may be divided into lipophilic or hydrophilic drugs according to their distribution coefficient. Atenolol, nadolol or sotalol are hydrophilic, penbutolol or propranolol are lipophilic whereas bisoprolol or betaxolol are in an intermediate position. The following parameters are dependent on lipophilicity: 1) duration of β-receptor blockade, 2) metabolism or renal elimination (pharmacokinetics), 3) diffusion through biological barriers (eg, blood/brain, placenta) and 4) tissue concentration (especially during intoxication).

Hydrophilic β-blockers like atenolol are advantageous in patients who suffer from central nervous side effects during therapy with lipophilic drugs (sleep disturbances, psychosis, depression, hallucination) [9].

Table 3: Patients in whom β_1-selectivity is advantageous

1. Obstructive lung disease
2. Smokers
3. Physically active patients (metabolism)
4. Diabetic patients
5. Patients with lipid disorders
6. Pregnancy
7. Portal hypertension
8. Drug interaction with involvement of β_2-receptors

Table 4: Pharmacokinetic properties of β-blockers

Substance	Resorption %	Bioavailability %	F.P.E.[1]	Act.[2] met.	PPB[3] %	V_d[13] l/kg
Acebutolol		40–60[9]	+	+[4]	11–25	1.35
Alprenolol	> 95	10–30[9]	+	+	80	3.3
Atenolol	50	50	–	–	3	0.7
Betaxolol	> 95	80	–	–	50	6.0
Bisoprolol	> 90	88	–	–	30	3.2
Bopindolol	> 95	60–70[7]	+	+	65[7]	2.9
Bupranolol	> 95	< 10	+[5]	+[5]	76	
Carazolol	> 85	< 10	+	–	81	10.9[8]
Carteolol	> 90	90	–	+	15	3.6
Carvedilol	85	25	+	+	98	2
Celiprolol	50	50[9]	–	–	25	6.5
Esmolol[11]				–	56	3.4
Mepindolol	> 95	> 95	–	–	50	5.7
Metipranolol[6]	> 95	50	+	+	70	3.5
Metoprolol	> 95	50[9]	+	–	12	5.6
Nadolol	30	20–30	–	–	25	2.5
Nebivolol	> 95	12[12]	+	+	98	?10
Oxprenolol	> 90	24–60	+	–	80	1.3
Penbutolol	> 90	> 90	–	–	95	0.3
Pindolol	90	90	–	–	60	2.0
Propranolol	> 90	30[9]	+	+	93	3.6
Sotalol	75–90	75–90	–	–	0	2.0
Talinolol	50–70	55[10]	–	–	60	3.3
Tertatolol	85	64	+		94	0.43
Timolol	90	50–75[9]	+	–	10	1.4–3.5

[1]) F.P.E. = first pass effect; [2]) Act. met. = active metabolite clinically relevant; [3]) PPB = plasma protein binding; [4]) diacetolol; [5]) carboxy-bupranolol (> 90 %); [6]) desacetyl-metipranolol is the active compound; [7]) hydrolysed bopindolol as active metabolite; [8]) results with radio-labeled carazolol; [9]) dose dependent biovailability; [10]) decrease of bioavailability by food intake; [11]) only i.v.-application; [12]) 96 % in slowly metabolizing individuals; [13]) V_d = volume of distribution.

Stereospecificity

With the exception of penbutolol or timolol all β-blockers are racemic mixtures containing 50 % of the β-receptor blocking S-isomer and 50 % of the R-isomer which is without β-blocking action. Introduction of the pure S-form into the market is without clinical significance as there is no evidence that concomitant application of the S- and R-form leads to a higher rate of side effects.

Haemodynamic actions

The acute action of β-adrenoceptor blocking drugs depends on their pharmacodynamic actions. Drugs without selectivity for β_1-receptors acutely increase peripheral resistance whereas β_1-selective drugs are almost completely without direct vascular actions. β-blockers with direct vasodilative effects decrease peripheral resistance. This holds true for celiprolol (β_2-ISA), carvedilol (additional α_1-antagonism) and nebivolol (activation of NO-synthase).

Pharmacokinetic properties

Pharmacokinetic differences of β-adrenoceptor blocking drugs (Tables 4 and 5) with respect to absorption in the gastrointestinal tract, liver metabolism, plasma protein binding, volume of distribution and renal or biliary elimination play an important role for those patients in whom these parameters are altered by their disease [1, 2]. Especially disturbances of hepatic and/or renal clearance may be of clinical significance either for the choice of the appropriate drug or for the dose regimen of a given drug.

Table 5: Pharmacokinetic properties of β-blockers

Substance	$t_{1/2}$[1] (h)	Renal elimination %[2] unchanged	total	Total clearance (ml/min)	Renal clearance (ml/min)
Acebutolol	7–13	< 10	25–54	600	200
Alprenolol	2–3	< 1	> 90	1200	≈ 0
Atenolol	6–9	47	47	100–180	100–170
Betaxolol	14–20	15	80	326	47
Bisoprolol	10–12	50	95	257	140
Bopindolol	10–14	?	50	515	?
Bupranolol	1–2[3])	0	> 90[3])		≈ 0
Carazolol	8[5])	< 0.2	< 10	3500[5])	10[5])
Carteolol	7	65	75	650	277
Carvedilol	7	< 2	15	600	≈ 0
Celiprolol	5	23.5	23.5	850	150
Esmolol	9	< 2	80	19950	≈ 0
Mepindolol	4.2	2	65–75	650	≈ 0
Metipranolol[4])	3	4	> 40	1237 (i.v.)	100
Metoprolol	3–4	3	> 97	1100	109
Nadolol	14–24	25	25	110	67
Nebivolol	22	< 0.5	36	860	7.4
Oxprenolol	1–3	< 5	70–95	600	≈ 0
Penbutolol	1–3[6])	< 1	> 90	350	≈ 0
Pindolol	3–4	40	> 90	400	163
Propranolol	3–4	< 1	> 90	1000	≈ 0
Sotalol	15	75–90	75–90	120	120
Talinolol	12	28	28	343	196
Tertatolol	3	< 1	55	130	≈ 0
Timolol	5.5	< 20	73	560	70–109

[1]) $t_{1/2}$ = plasma half life (ß-phase) after oral application; [2]) % of dose; [3]) carboxy bupranolol; [4]) desacetyl-metipranolol as active drug; [5]) radio-labeled carazolol; [6]) penbutolol has a terminal plasma half life (γ-phase) of 27 hours.

Absorption

Absorption of β-adrenoceptor blocking drugs occurs rapidly so that maximal plasma levels are reached within 1–3 h. Lipophilic agents like penbutolol, propranolol, oxprenolol or alprenolol as well as less lipophilic drugs such as betaxolol, bisoprolol, pindolol or metoprolol (Table 2) are almost completely absorbed from the gastrointestinal tract. On the other hand, hydrophilic drugs such as atenolol are incompletely absorbed. Bioavailability of the drug is about 50 % because a considerable amount is excreted via the faeces.

Hepatic clearance

Because of a high first-pass metabolism (Table 4) about 90 % of oral alprenolol, 70 % of propranolol or 50 % of metoprolol and oxprenolol are transferred to their inactive or active (eg, propranolol) metabolites. Total clearance of these drugs ranges from 600 to 1,200 ml/min which is in the order of magnitude of the hepatic blood flow and reflects complete elimination in the liver with a renal clearance of about zero.

Some of the drugs with a high first-pass effect show dose dependency of bioavailability [10]. There is a low bioavailability for doses of propranolol less than 20 mg. Above 40 mg the drug shows a linear increase in bioavailability with increasing dose. Slow release preparations of drugs with a high first-pass effect and a dose-dependent bioavailability, therefore, might show relatively low plasma concentrations. On the other hand, oxprenolol with a high presystemic elimination rate that is independent of dose has been demonstrated to possess an unchanged bioavailability if it is transferred to a slow release form [11].

The first-pass metabolism may show high interindividual variations and hence why remarkable differences in plasma

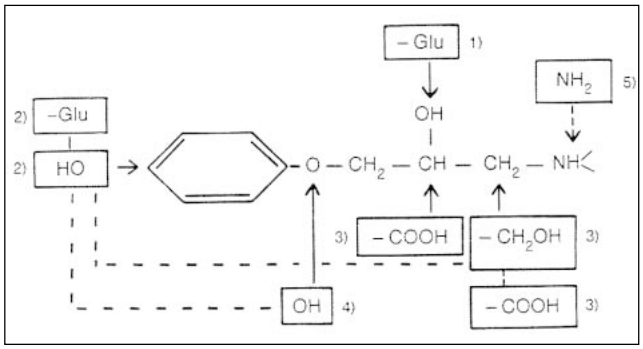

Figure 1: Metabolic pathways of ß-adrenoceptor blocking drugs in the liver. Glu = Glucuronide. The numbers indicate the following metabolic pathways: 1) Glucuronidation of the drug at the OH group of the side chain. 2) Aromatic hydroxylation and subsequent glucuronidation partly combined with the steps described under 3 and 4 (---). 3) Oxidative desamination. 4) Ether cleavage to phenol. 5) N-desalcylation.

levels can be observed between patients who take the same dose. While differences in plasma levels normally range from 1:2 to 1:6, they may amount to 1:10 for metoprolol or alprenolol or even to 1:20 for propranolol [12].

The most common metabolic pathways of β-adrenoceptor blocking drugs in man are summarised in Figure 1. Glucuronidation of the drug is the only and nearly completely performed metabolic step for oxprenolol and penbutolol. The glucuronide which is vial of β-sympatholytic action *in vitro* is excreted via the kidneys. A pronounced metabolism is also observed with betaxolol, metoprolol and timolol.

Bisoprolol is eliminated by about 50 % in the liver and 50 % in the kidneys (balanced clearance). Similar conditions have been reported for pindolol. In patients suffering from liver cirrhosis and ascites plasma half-life is increased to about 15 h compared with 10 h in normal subjects (Figure 2). This means that the normal dose can be used in these patients.

Acebutolol is transformed into the hydrophilic active metabolite diacetolol, which during long-term treatment amounts to 70 % of the bioavailable portion of acebutolol, and diacetolol is therapeutically important. It is almost completely eliminated via the kidneys, and this has to be taken into account in patients with kidney disease or in old patients. In addition, diacetolol shows a higher β_1-selectivity, lower partial agonist activity and a longer plasma half-life than acebutolol [14].

Those drugs that are mainly eliminated by the liver by oxidative metabolism such as propranolol, metoprolol or

Figure 2: Mean plasma concentrations of bisoprolol (ng/ml) after repeated oral application of once daily 10 mg bisoprolol in volunteers (——, n = 8, $t_{1/2}$ = 10.0 h), patients with liver cirrhosis (---, n = 8, $t_{1/2}$ = 11.8 h) and patients with liver cirrhosis and ascites (•••, n = 5, $t_{1/2}$ = 15.3 h). Taken from Kirch et al [13].

Table 6: Maximal daily dose of hydrophilic β-blockers in renal failure. According to Knauf et al. [15]

β-blocker	Creatinine clearance (ml/min)	Serum creatinine (mg %)	Initial dose (mg)	Maintenance dose (mg)
Atenolol	> 30	< 2.5	100	100
	10–30	2.5–5	100	50
	< 10	> 5	100	25
Carteolol	> 30	< 2.5	10	10
	10–30	2.5–5	10	5
	< 10	> 5	10	2.5
Nadolol	> 30	< 2.5	120	120
	< 30	> 2.5	120	60
Sotalol	> 30	< 2.5	160	80
	< 30	> 2.5	160	25

oxprenolol may interact with cimetidine, proton pump inhibitors (eg, omeprazol) or the $I_{Ca,T}$-channel blocker mibefradil, that are known to inhibit enzymatic oxidation. Therefore, these β-adrenoceptor blockers should either be given in a reduced dose or replaced by blockers not metabolised in the liver (eg, atenolol). Otherwise cimetidine may be replaced by ranitidine and famotidine, respectively, or mibefradil by eg, amlodipine. Dose adjustment for β-adrenoceptor blockers with a high hepatic clearance is recommended in patients with decreased liver function.

Renal clearance

Hydrophilic β-adrenoceptor blocking drugs like atenolol, nadolol or sotalol are mainly eliminated via the kidneys (Table 5). Their renal clearance amounts to 100–170 ml/min and is not different from total clearance which reflects renal elimination by glomerular filtration. There is a linear correlation between renal clearance and the glomerular filtration rate of these drugs [15]. If kidney function is reduced, renal clearance of atenolol, carteolol, diacetolol, nadolol or sotalol is decreased and plasma half-life is increased. In patients with severe renal failure (clearance < 10 ml/min), the plasma half-life is prolonged to 40–45 h [15]. As a consequence, the dose must be adjusted to the degree of renal failure (Table 6). The hydrophilic drugs listed in Table 6 may be dialysed as they show a low plasma protein binding and a relatively low volume of distribution. Plasma half-life measured during dialysis is in part lower than in normal subjects.

Figure 3: Mean plasma concentrations of bisoprolol (ng/ml) after repeated oral application of once daily 10 mg bisoprolol in volunteers (——, n = 8, $t_{1/2}$ = 10.0 h), patients with moderate impairment of renal function (—, n = 6, $t_{1/2}$ = 16.2 h) and patients with severe renal dysfunction (· · ·, n = 4, $t_{1/2}$ = 19.7 h). Taken from Kirch et al [13].

Elimination of lipophilic β-adrenoceptor blocking drugs such as propranolol is largely independent of kidney function. However in the case of propranolol, accumulation of metabolites has been observed in patients with renal failure [15]. The plasma level of propranolol-glucuronide is increased 18-fold, that of 4-OH propranolol glucuronide 29-fold and that of naphthoxy-lactic acid 29-fold. It is still an unsolved question whether high concentrations of these metabolites have pharmacodynamic actions *in vivo*.

Renal elimination of pindolol amounts to about 95 % of the oral dose, 40 % as unchanged drug and 55 % as metabolites. Severe renal failure leads to an increase in elimination half-life by a factor of 1.4 [16]. Compared with a factor of 4 for diacetolol or atenolol and a factor of 6 for sotalol, accumulation of pindolol can be regarded as not critical. Similar results have also been observed for bisoprolol and betaxolol. As already mentioned, half of the oral dose of bisoprolol is eliminated via the kidneys as unchanged bisoprolol, the other half as inactive metabolites. Severe impairment of renal function leads

Figure 4: Effects of 10 mg bisoprolol and 100 mg metoprolol on systolic blood pressure (SBP), heart rate (HR) and the rate pressure product (RPP) during and after ergometry: before (basal: b) and after 4 weeks of ß-blocker therapy, 24 and 3 h after application (x ± SEM; n = 44). The areas between the baseline curves (b) and the 24 h p.a. curves are significantly larger with bisoprolol than with metoprolol. The hatched areas between the exercise curves 3 h p.a. and 24 h p.a. are a measure of the loss of effect after 24 h. The smaller this area, the greater is the residual effect after 24 hours. Taken from Haasis and Bethge [17].

Table 7: Side effects of β-blockers

Heart	Bradycardia, SA- or AV-block. After acute termination of ß-blockade: angina pectoris
Circulation	Hypotension, disorder in peripheral circulation (cold extremities), increase in blood pressure in phaeochromocytoma
Air-ways	Obstruction (dyspnoea), especially in bronchial asthma
Intestine	Diarrhoea, spasm, nausea, vomiting
Urogenital tract	Motility of uterus ↑, disorder of miction, impotence
Sceletal muscle	Weakness, muscle cramps
CNS	Sleep disturbances, nightmares, fatigue, hallucination, depression (rare), dizziness
Metabolism	Hypoglycaemia, HDL ↓, VLDL ↑
Skin	Sweating, erythema, paraesthesia, allergic reactions, psoriasis, alopecia
Eye	Irritation symptoms of the conjunctiva, decrease in lacrimal fluid (cave: contact lenses)

to an increase in plasma half-life of up to a maximum of two-fold (Figure 3). Decrease in renal clearance down to 10 ml/min does not require a change in the dose regimen of bisoprolol or betaxolol.

Duration of action

Binding studies with β-adrenoceptor blocking drugs in the presence of human plasma in combination with investigations of the sympatholytic activity in volunteers have shown that there is a correlation between plasma levels and drug action [4, 5]. This is of major importance for the duration of action which depends on dose and plasma half-life. It has been demonstrated in hypertensive patients that 10 mg of bisoprolol p.o. reduce blood pressure, heart rate and the rate pressure product (blood pressure x heart rate) over 24 h whereas the action of 100 mg metoprolol is not maintained over this interval (Figure 4). These observations may be of clinical significance as patients with coronary heart disease who take their drug once a day in the morning need protection for the rest of the day. It is known that the incidence of silent ischaemic episodes, myocardial infarctions and strokes increases in the early morning hours. Therefore, a preferential drug would guarantee a full therapeutic effect for 24 h. In accordance with this strategy, metoprolol is available as slow release formulation.

In summary, the different pharmacokinetic properties of β-adrenoceptor blocking drugs are of great importance for those patients who suffer from either liver or kidney disease. Furthermore, a long plasma half-life is essential in those patients who need therapeutic actions for 24 h, but who take the drug once a day.

Side effects

Typical side effects of β-blockers are summarised in Table 7. Drugs with β_1-selectivity show a lower incidence of side effects due to inhibition of β_2-receptors [6]. This is of particular clinical significance for the impairment of the airways, circulation, the urogenital tract as well as metabolism, β-blockers used in pregnancy or in smokers should be β_1-selective. Disorders of the CNS may be avoided by using hydrophilic drugs such as atenolol. Decrease in peripheral resistance can be achieved by vasodilating β-blockers like celiprolol, nebivolol or carvedilol.

β-blockers are contraindicated in sick sinus syndrome, pathological bradycardia (< 50 beats/min), 3rd degree AV-block, hypotensive shock syndromes, bronchial asthma, trophic disorders of the cornea or drug-specific allergy.

References

1. Frishman WH. Clinical pharmacology of the beta-adrenoceptor blocking drugs. Appleton-Century-Crofts, New York 1980.
2. Borchard U. β-Rezeptorenblocker. Klinik und Praxis. Aesopus-Verlag, Basel 1988.
3. Bristow MR, Ginsburg R, Umans V et al. β_1- and β_2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective β_1-receptor down-regulation in heart failure. Circ Res 1986; 59: 297.
4. Wellstein A, Palm D, Belz GG et al. Receptor binding of propranolol is the missing link between plasma concentration kinetics and effect time course in man. Eur J Clin Pharmacol 1985; 29: 131–47.
5. Wellstein A, Palm D, Belz GG. Affinity and selectivity of β-adrenoceptor-antagonists in vitro. J Cardiovasc Pharmacol 1986; 8 (Suppl. II): 36–40.
6. Simpson WT. Nature and incidence of unwanted effects with atenolol. Postgrad Med J 1977; 53: 162.
7. Lohmöller G, Conca W, Pötzl CH. Klinische Bedeutung der ISA des Betablockers Carteolol. Med Klin 1987; 82: 47.
8. Yusuf S, Peto R, Lewis J, Collings R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Progr Cardiovasc Dis XXVII 1985; 335.
9. Greminger P, Vetter H, Boelin HJ, Baumgart P, Havelka J, Walger P, Lüscher T, Siegenthaler W, Vetter W. Atenolol, Pindolol und Propranolol bei essentieller Hypertonie: Ansprechquote und Verträglichkeit. Schweiz med Wschr 1982; 112: 1831.
10. Shand D, Rangno R. Disposition of propranolol. I. Elimination during oral absorption in man. Pharmacology 1972; 7: 159–68.
11. Ries W, Brechbühler S, Brunner L, Imhof P, Hack DB. Der Metabolismus von betaadrenolytischen Substanzen im Zusammenhang mit ihrem pharmakokinetischen und -dynamischen Verhalten. Therapiewoche 1975; 25: 4259–69.
12. Johnsson G, Regardh C-G. Clinical pharmacokinetics of β-adrenoceptor blocking drugs. Clin Pharmacokinet 1976; 1: 233–63.
13. Kirch W, Rose I, Demers HG et al. Pharmacokinetics of bisoprolol during repeated oral administration to healthy volunteers and patients with kidney or liver disease. Clin Pharmacokinet 1987; 3: 110–7.
14. Borchard U, Hafner D, Hirth C. Pharmacological properties of diacetolol, the major metabolite of acebutolol in man. In: Lichtlen, Maranhao (eds). Advances in β-blocker therapy III. Schattauer, Stuttgart 1983; 29–39.
15. Knauf H, Schäfer-Korting M, Mutschler E. Pharmakokinetik und biologische Wirkdauer von β-Rezeptorenblockern bei Niereninsuffizienz. Internist 1981; 22: 616–21.
16. Ohnhaus EE, Münch U, Meier J. Vergleichende Untersuchung zur Elimination von Pindolol (Visken) und Antipyrin bei Patienten mit Lebererkrankungen. Schweiz med Wschr 1976; 106: 1748–58.
17. Haasis R, Bethge H. Exercise blood pressure and heart rate reduction 24 and 3 hours after drug intake in hypertensive patients following 4 weeks of treatment with bisoprolol and metoprolol: A randomized multicenter double-blind study (BISOMET). Eur Heart J 1987; 8 (suppl. M): 103–11.

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