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Balanced Pharmacokinetics and Metabolism of Bisoprolol

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Summary: Bisoprolol exhibits a high absolute bioavailability (90%) because of its nearly complete absorption (>90%) and small first-pass effect (10%). Bioavailability is independent of food intake. A long plasma-elimination half-life (10–11 h) allows a once-a-day dose regimen. Because of the low plasma protein-binding (30%), kinetics are insensitive to protein-binding interactions. The balanced clearance (equieffective hepatic and renal clearance) renders the kinetics virtually insensitive to renal or hepatic insufficiency. Even in the case of complete failure of one clearance organ, the plasma elimination half-life of bisoprolol would only double. The metabolites that are inactive and do not accumulate are eliminated predominantly by the kidneys. There is no stereoselective metabolism. The metabolism of bisoprolol is insensitive to liver enzyme inhibition (cimetidine), and nearly insensitive to liver enzyme induction (rifampicin). The metabolism is independent of genetic oxidation-polymorphism (debrisoquine). The pharmacokinetics of bisoprolol are independent of the dose in the range from 2.5 to 100 mg. There is no age or sex dependency. Bisoprolol exhibits predictable pharmacokinetics with well-balanced properties leading to small intra- and interindividual variability of the plasma concentration time curves and pharmacokinetic parameters. Bisoprolol is the β-blocker with LADME(liberation, absorption, distribution, metabolism, and elimination)-optimized pharmacokinetics. This is a prerequisite for therapeutic reliability. **Key Words:** Bisoprolol — β_1-Selective adrenoceptor antagonist — Pharmacokinetics — Metabolism — Bioavailability.

Because the pharmacokinetics of bisoprolol already have been extensively investigated, it is only possible to present an overview. One possible means of differentiating β-adrenoceptor antagonists is to classify them according to their in vitro partition behaviour as either lipophilic or hydrophilic. In this respect, bisoprolol takes an intermediate position. It is very soluble in water and methanol, and has good solubility in ethanol and chloroform. The partition coefficient (PC) of bisoprolol is 4.8 at pH 7.4 in *n*-octanol/phosphate buffer (37°C), and 1.09 at pH 7.0 and 2.6 at pH 7.4 in *n*-octanol/Davis universal buffer (37°C).

It is justifiable to say that bisoprolol is as soluble in water as it is in organic solvents, or that it is as lipophilic as it is hydrophilic. This balanced in vitro partition behaviour is certainly the basis for the balanced pharmacokinetic properties that bisoprolol exhibits in humans.

It is well known that lipophilic β-blockers very often fail to display a high bioavailability because of an extensive first-pass effect, while on the other hand hydrophilic β-blockers show less bioavailability because of poor enteral absorption. Bisoprolol is readily and virtually completely absorbed (>90%), and because of its moderate hepatic metabolism, it is only subject to a very small hepatic first-pass metabolism (<10%). Therefore, bisoprolol displays a high bioavailability of 90% of an oral dose. This statement results from the following observations: The basic pharmacokinetics of bisoprolol have been studied in five healthy volunteers following oral ingestion of 20 mg ^{14}C-bisoprolol (2.9 *M*Bq/subject) (1). The cumulative renal and faecal elimination of total radioactivity add up to >90% of the dose (Fig. 1).

The absolute bioavailability of 10 mg bisoprolol tablets has been determined in a crossover study with 12 healthy volunteers (1). Figure 2 shows the mean plasma concentration time course of bisoprolol after i.v. and oral administration. The absolute bioavailability, assessed by three different methods, was found to be 88%. Other pharmacokinetic parameters assessed in these two studies are shown in Table 1. The mean ($\bar{x} \pm$ SEM) elimination half-lives were $t_{1/2\beta} = 10.3 \pm 0.6$ and 11.0 ± 0.9 h, following oral and i.v. administration, respectively. This elimination half-life is ideal for a once-a-day dose regimen, thus also opti-

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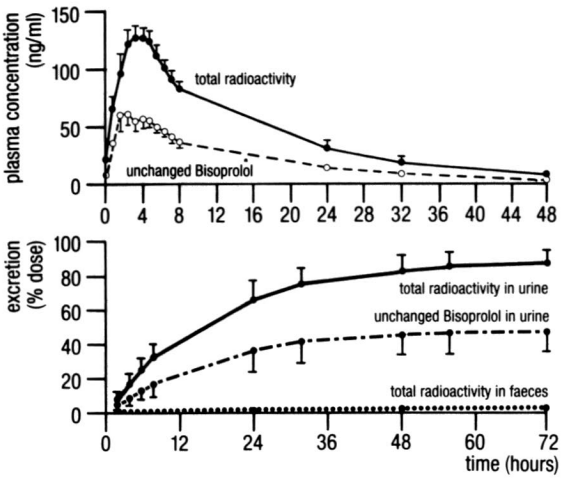

FIG. 1. Plasma concentration time curves and cumulative renal and fecal excretion of bisoprolol and total radioactivity after oral administration of 1 × 20 mg ^{14}C-bisoprolol (2.9 *M*Bq/subject) as aqueous solution to five healthy male volunteers. Mean ±SD. Bisoprolol measured by specific HPLC-method with a detection limit of 1–2 ng/ml (7). Total radioactivity calculated as ng Eq. bisoprolol.

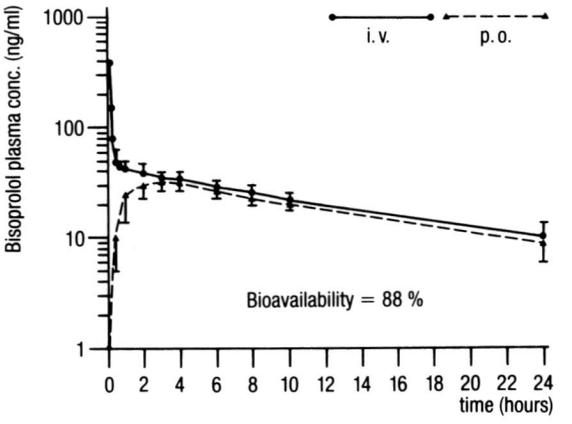

FIG. 2. Mean plasma concentration time curves of 10 mg bisoprolol after i.v. and oral administration of 10 mg to 12 healthy male volunteers. Crossover design. Mean ±SD. For assay of bisoprolol, see legend of Figure 1. Absolute bioavailability was 88 ± 6%, calculated by three different methods: $AUC_{0-\infty}$ p.o. × 100/$AUC_{0-\infty}$ i.v.; $AUC_{0-\infty} \times k_e$ p.o. × 100/$AUC_{0-\infty} \times k_e$ i.v., and $U_{0-48\,h}$ p.o. × 100/$U_{0-48\,h}$ i.v.; In vitro dissolution characteristics of the film-coated tablets were disintegration within 2–5 min and dissolution within 15 min. The method used was USP apparatus II (paddle), 100 rpm.

mizing the patient compliance. It is also important to note that the high bioavailability is independent of the fasting state or when food is administered (Fig. 3).

The next pharmacokinetic feature which has to be addressed in the context of balanced pharmacokinetics is the clearance. It is well known that lipophilic β-blockers are predominantly cleared by hepatic metabolism, whereas hydrophilic β-blockers exhibit predominantly renal clearance. Again, bisoprolol takes an intermediate position. The disposition of bisoprolol is characterized by the fact that the metabolic and renal clearance of this substance in humans are virtually equal in extent (1).

After i.v. administration, the following clearances were observed: for Cl_{tot} 0.2 ± 0.01 l/h/kg and for Cl_{ren} 0.12 ± 0.01 l/h/kg ($\bar{x}$ ± SEM).

Since after oral administration ~10% of the dose is subject to first-pass metabolism, ~50% of an oral dose is excreted with the urine as unchanged bisoprolol, whereas ~50% is metabolized (Fig. 1, Table 1). In

TABLE 1. *Pharmacokinetic parameters of bisoprolol in humans following intravenous injection and single oral dose in solution and tablet formulation*

	Oral solution	IV injection	Tablet
Dose (mg)	20	10	10
c_{max} (ng/ml)	70 ± 20	—	36 ± 7
t_{max} (h)	2.7 ± 1.6	—	3.0 ± 1.0
$t_{1/2\beta}$ (h)	10.6 ± 3.0	10.3 ± 1.9	11.0 ± 3.1
$AUC_{0-\infty}$ (ng · ml^{-1} · h)	1,017 ± 280	672 ± 165	598 ± 134
Urinary excretion (% of dose)			
Bisoprolol	47.8 ± 10.5	62.5 ± 7.8	55.1 ± 10.2
Bisoprolol + metabolites[a]	90.0 ± 6.0	—	—
Cl_{tot} (l/h)	18.2 ± 4.9	15.6 ± 3.2	15.4 ± 3.1
Cl_{ren} (l/h)	8.9 ± 3.8	9.6 ± 1.6	8.4 ± 2.1
Absorption[a] (% of dose)	>90	—	—
Absolute bioavailability[b] (% of dose)	—	100	88 ± 6
$V_{d\ area}$ (l)	269 ± 64	226 ± 37	235 ± 44

Mean ±SD.
Values given based on unchanged bisoprolol.
[a] Based on total radioactivity data (ng Eq bisoprolol).
[b] Absolute bioavailability calculated by three different methods (see legend of Fig. 2).

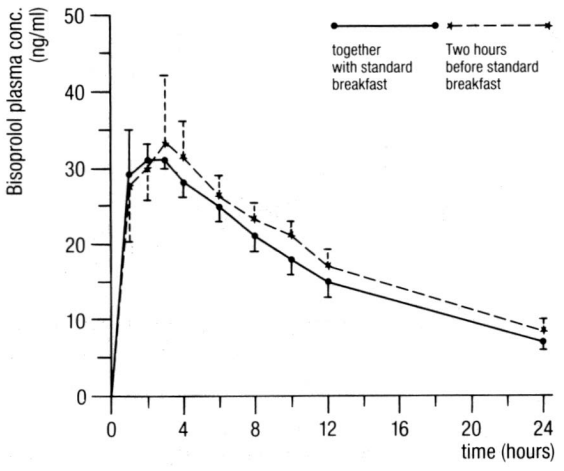

FIG. 3. Influence of food on the plasma concentration time course of bisoprolol following single oral administration of 10 mg to six healthy male subjects. Crossover design; $\bar{x} \pm SD$. For assay of bisoprolol, see legend of Figure 1.

other words, bisoprolol is cleared by the kidneys as well as by the liver, thus having two equieffective clearance routes. This phenomenon of a balanced clearance is of special clinical relevance. The elimination half-life ($t_{1/2}$) is directly proportional to the distribution volume (V_d), and inversely proportional to the total body clearance (Cl_{tot}):

$$t_{1/2} = \frac{\ln 2 \cdot V_d}{Cl_{tot}}$$

In addition, as Cl_{tot} is made up of the metabolic clearance (primarily hepatic, Cl_{metab}) and the renal clearance (Cl_{ren}),

$$t_{1/2} = \frac{\ln 2 \cdot V_d}{Cl_{metab} + Cl_{ren}}$$

In the case of a balanced clearance, Cl_{metab} and Cl_{ren} are equal in size

$$Cl_{metab} = Cl_{ren}$$

Because of the property of a balanced clearance, even in the case of a complete failure of one clearance organ, the plasma elimination half-life of bisoprolol can only double. This means that in renal or hepatic insufficiency, it is virtually unnecessary to adjust the dosage of bisoprolol.

In the meantime, this hypothesis has been tested successfully in patients with different stages of renal insufficiency (2). Even in patients with terminal renal failure who are on hemodialysis, only a mean elimination half-life of bisoprolol of 24 h was observed during periods free of hemodialysis (H.G. Demers, unpublished observations). During a 4-h period of haemodialysis, 5% of a dose of bisoprolol is eliminated as unchanged bisoprolol. So, also in these patients, the daily dose of bisoprolol should be 5–10 mg, which is in fact part of the normal therapeutic dose range.

In patients with different stages of liver cirrhosis, a prolongation of the elimination half-life of bisoprolol by less than a factor of 2 was observed (2).

Thus, the advantage of the balanced clearance of bisoprolol could be shown in clinical practice. The consequence of this special property (i.e., two equieffective clearance routes) is that it is not necessary to adjust the dose of bisoprolol either for patients with impaired renal function or for patients with impaired liver function. Only in patients with chronic terminal failure of one of the two organs should the maximum daily dose of bisoprolol be limited to 10 mg, a dose that represents the predominant therapeutic dose anyway.

The metabolism of bisoprolol in humans also has several features which constitute clinical advantages. Bisoprolol is subject only to moderate hepatic metabolism. With a hepatic clearance of ~100 ml/min, bisoprolol does not belong to the hepatic high-clearance drugs, which is the reason for the very small first-pass effect observed. In the metabolism of bisoprolol, only oxidative pathways have been detected, with no subsequent conjugation (Fig. 4). All metabolites in humans are pharmacologically inactive and, being very polar, are eliminated by the renal route. The β-adrenoceptor antagonistic metabolite M 4, known only slightly, could not be detected in humans (3,4).

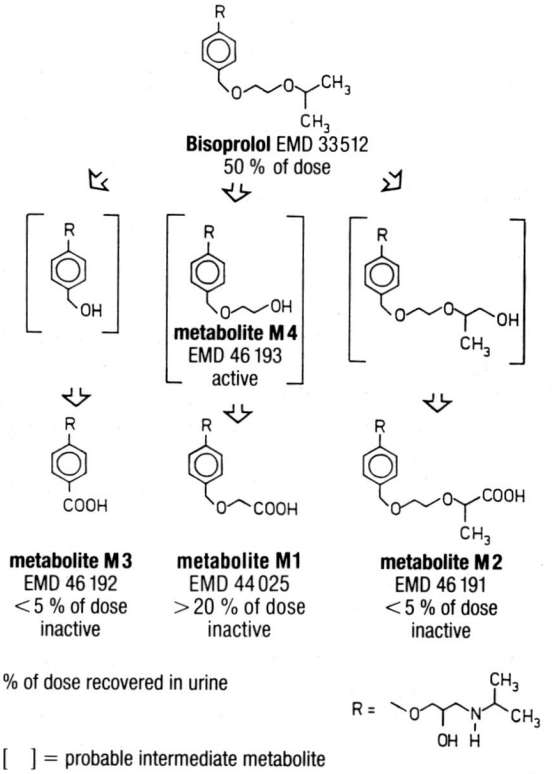

FIG. 4. Metabolism of bisoprolol in humans.

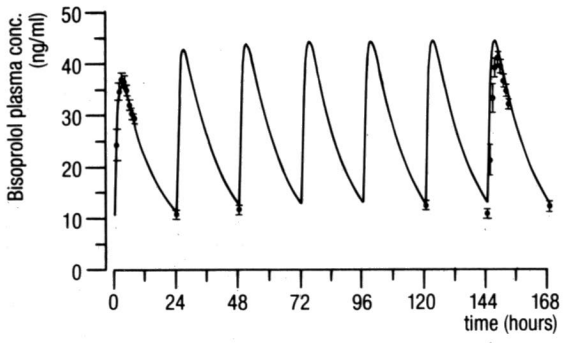

FIG. 5. Mean plasma concentration time course of bisoprolol in 10 healthy male volunteers under 10 mg bisoprolol once-a-day over 7 days. $\bar{x} \pm$ SEM. For bisoprolol assay, see legend of Figure 1. Accumulation factor of 1.2 was calculated by two different methods: AUC_τ 7th day/AUC_τ 1st day, and U_τ 7th day/U_τ 1st day.

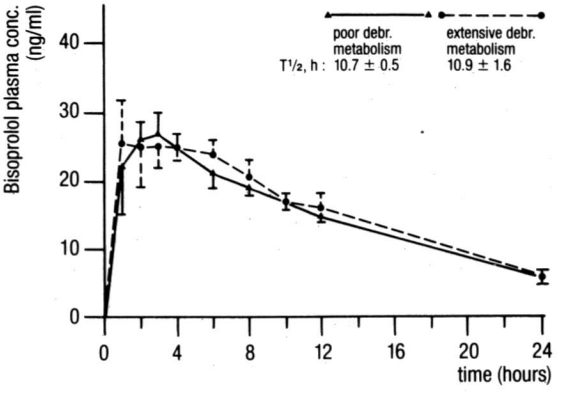

FIG. 6. Plasma concentration time curves of bisoprolol following single oral administration of 10 mg to healthy subjects with extensive and poor debrisoquine metabolism. (Mean, SEM, n = 5). For bisoprolol assay, see legend of Figure 1.

In a study with ^{14}C-bisoprolol it has been shown that the elimination half-life of the total radioactivity is ~12 h. So it is quite clear that the metabolites of bisoprolol will not accumulate under the once-a-day dose-regimen — at least not more than bisoprolol itself. Administered once a day, bisoprolol, with its elimination half-life of 10-12 h, has an accumulation factor of 1.2 (Fig. 5). With single daily administration, the accumulation (factor, 1.2) virtually compensates for the first-pass effect (factor, 0.88), and thus the body load in any dosing interval is equal to the administered dose.

Because of its moderate hepatic metabolism, bisoprolol should not be sensitive to interactions with other drugs on the basis of liver enzyme inhibition or induction. This has been demonstrated clinically with cimetidine as a very potent inhibitor of hepatic drug metabolism, and with rifampicin as a very potent inducer of hepatic drug metabolism (5). The mean plasma concentrations of bisoprolol, under steady-state conditions, after bisoprolol alone (10 mg once-a-day) and coadministration of either cimetidine (400 mg TID) or rifampicin (600 mg once-a-day), have been measured, followed by calculation of the relevant pharmacokinetic parameters. The elimination half-lives and the total clearances of bisoprolol with and without simultaneous cimetidine treatment were not significantly different.

On the other hand, the relatively slow biotransformation rate of bisoprolol can, to a certain degree, be induced. Rifampicin is able to shorten the elimination half-life of bisoprolol, on average, to 6.2 h. But since in the presence of this very strong enzyme inducer the elimination half-life is shortened only by ~35%, interactions with usually less strongly inducing drugs will not be clinically relevant.

In hyperthyroid states, no enhancement of the metabolism of bisoprolol could be observed (6). In this context, it should be mentioned that drug interactions due to displacement from plasma proteins are not to be expected either because of the low degree of protein-binding of bisoprolol (30%) (4).

Furthermore, the metabolism of bisoprolol shows no stereoselectivity and also no genetic oxidation-polymorphism of the debrisoquine type (Fig. 6).

Judging from all the points mentioned previously, the metabolism of bisoprolol does not give rise to great pharmacokinetic variability, which is a well-known problem with many other β-blockers.

The next issue to be raised is the dose dependency of the pharmacokinetics of bisoprolol. In several studies in different parts of the world, a wide dose range of bisoprolol, i.e., from 2.5 to 100 mg, has been investigated. Figure 7 summarises all the results. Even these data, obtained from nonhomogeneous populations and without normalising for weight, demonstrate, at first glance, that bisoprolol exhibits linear pharmacokinetics,

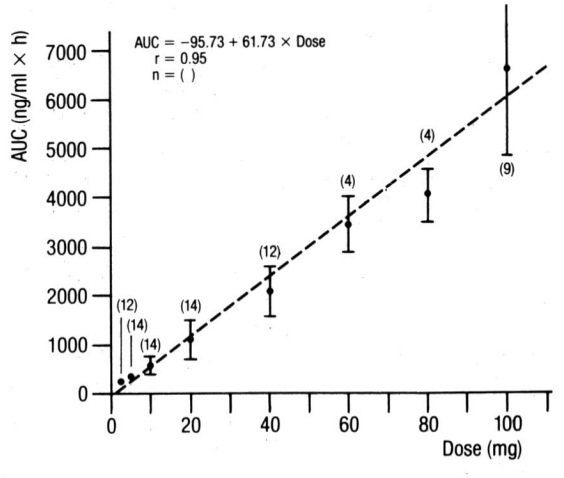

FIG. 7. Synopsis: linear relationship between areas under plasma concentration time curves (AUC) and dose of bisoprolol from different studies. (Mean, SD).

Patient No.	Dose	
	10 mg	20 mg
1	46.1	85
2	48.4	101.9
3	50.1	106.9
4	56.6	109.6
5	55.1	99.7
6	43.6	108.6
7	49.9	112.8
8	42.3	82.9
mean	49.0	100.9
S.D.	5.07	11.3
CV %	10.3	11.2

FIG. 8. Bisoprolol plasma concentrations in eight CHD patients on the 2nd day, 2 h after oral administration of 10 and 20 mg for 2 days each. CV, Coefficient of variation.

which is another prerequisite for the easy handling of a drug in therapeutic use.

The favourable pharmacokinetic features of bisoprolol altogether lead (especially for a β-blocker) to very small intra- and interindividual variation in plasma concentration time courses, as well as in pharmacokinetic parameters. Figure 8 demonstrates this for the doses 10 and 20 mg, administered orally. This feature also can be derived from Figure 2, where SD is shown in the graph.

It is justified to say that, with respect to the biopharmaceutic aspects of LADME (liberation, absorption, distribution, metabolism, and elimination), bisoprolol is the β-blocker with optimized pharmacokinetics.

Figure 9 gives a synopsis of the pharmacokinetic profile of bisoprolol, pointing out the most important favourable features, their kinetic consequences, and their clinical relevance. Bisoprolol, being insensitive to a great number of factors that can augment the intra- and interindividual variability of pharmacokinetic parameters, monotonously exhibits under a constant daily dosage virtually identical plasma concentration time courses. Robust kinetics are a prerequisite for constant efficacy and for high therapeutic reliability.

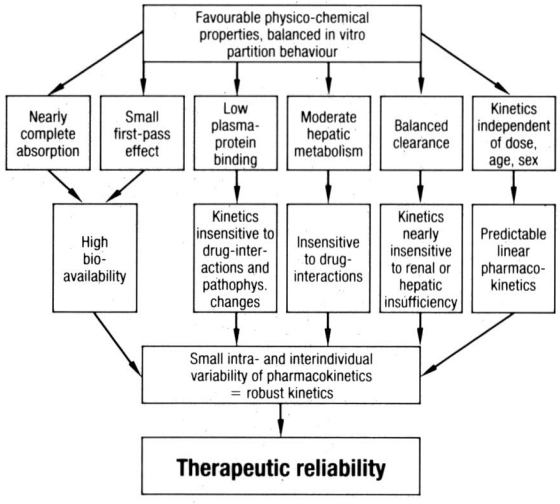

FIG. 9. Pharmacokinetic profile of bisoprolol.

REFERENCES

1. Leopold G, Pabst J, Ungethüm W, Bühring KU. Phase I studies on EMD 33 512, a new β_1-selective adrenoceptor blocking agent. *Clin Pharmacol Ther* 1982;31:243.
2. Kirch W, Rose I, Demers HG, Leopold G, Pabst J, Ohnhans EE. Pharmacokinetics of bisoprolol during repeated administration to normal subjects and patients with kidney or liver disease. *Clin Pharmacokin* 1987.
3. Bühring KU, Steiner K, Sailer H et al. Metabolism of the new betablocker bisoprolol in man, monkey, dog and rat (in press).
4. Bühring KU, Sailer H, Faro HP, Leopold G, Pabst J, Garbe A. Pharmacokinetics and metabolism of bisoprolol-^{14}C in three animal species and in humans. *J Cardiovasc Pharmacol* 1986;8 (suppl 11):S21–8.
5. Kirch W, Pabst J, Rose I, Klingmann I, Ohnhaus EE. Interaction of bisoprolol with cimetidine and rifampicin. *Eur J Clin Pharmacol* 1986;31:59–62.
6. Pfannenstiel P, Rummeny E, Baew-Christow Th et al. Pharmacokinetics of bisoprolol and influence on serum thyroid hormones in hyperthyroid patients. *J Cardiovasc Pharmacol* 1986;8(suppl 11):S100–5.
7. Bühring KU, Garbe A. Determination of the new β-blocker bisoprolol and of metoprolol, atenolol and propranolol in plasma and urine by high performance liquid chromatography. *J Chromatogr/Biomed Appl* 1986;382:215–24.