β -Adrenoceptor-Blocking Agents: Pharmacokinetic Differences and Their Clinical Implications Illustrated on Pindolol

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Quite a number of β -adrenoceptor-blocking drugs are available today for the treatment of hypertension and other cardiovascular disorders. Since β -blockers are drugs which are used in chronic treatment, the question of their long-term efficacy and safety has been of great interest and concern. It is, therefore, justified to compare the pharmacokinetic properties of the most frequently studied substances: acebutolol, alprenolol, atenolol, labetalol, metoprolol, nado-lol, oxprenolol, penbutolol, pindolol, practolol, propranolol, sotalol and timolol. The pharmacokinetics of the β -blockers are important and relevant because there are clear relations between their plasma concentrations and their effects, e.g. in exercise-induced tachycardia (1, 2) and for antihypertensive effect (3).

'Ideal' Pharmacokinetics

Since there are many β -blockers available with very similar pharmacological profiles, it is desirable to choose a β -blocker with favorable or ideal pharmacokinetics due to the necessary chronic treatment – quite often in combination with many other drugs – and due to their frequent use in patients with other disorders like renal, hepatic or cardiac insufficiencies. Table I lists 12 pharmacokinetic criteria which can be anticipated for an 'ideal' substance. These criteria are based on ecological considerations of drug treatment (e.g. dosage, good absorption and oral bioavailability), on predictability and small variability of plasma levels (e.g. small first-pass effect, dose-linearity), on practical experimental conditions (methodologies, correlations with pharmacodynamics) and on

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Table I. Pharmacokinetic criteria for ideal drug

Criterium

Specific, sensitive bioanalytical methodology

Once daily application possible

Small daily dose (< 50 mg/day)

Good absorption (> 80%)

Small first-pass effect « 20%

High absolute oral bioavailability (> 80%)

Small or moderate protein binding (< 80%)

Known correlation between plasma levels and effects

Linear pharmacokinetics valid

Steady-state plasma levels predictable from first dose

Metabolites no more active or toxic

Balanced clearance between liver and kidney

Table II. How the 13 β -adrenoceptor-blocking agents meet the 12 pharmacokinetic criteria of

table I	β -Blocker	Criterion	Σ	+	7	8	9	10	11	12
1	2	3	4	5	6					

Acebutolol

+

+

-

-

+

-

+

+

+

+

-

+

8

Alprenolol

+

-

-

+

-

-

-

+

-

-

-

-

3

Atenolol

+

+

-

-

+

-

+

+

+

+

+

-

8

Labetalol

+

-

-

+

-

-

?

+

+

-

-

-

4

Metoprolol

+

+

-

+

-

-

+

+

+

+

+

-

8

Nadolol

+

+

-

-

+

-

+

+

+

+

+

-

8

Oxprenolol

+

+

-

+

-

-

+

+

+

+

+

-

8

Penbutolol

+

+

+

+

?

7

1

-

+

9

-

-

5

Pindolol

+

+

+

+

+

+

+

+

+

+

+

+

12

Practolol

+

+

-

+
+
+
+
+
+
+
+

-

10

Propranolol

+

-

-

+

-

-

-

+

-

-

-

3

Sotalol

+

+

-

+

+

+

+

+

+

+

+

+

11

Timolol

+

+

+

+

+

-

+

+
+
+
+
+

11

+ = Criteria fulfilled; – = criteria not fulfilled; ? = not known yet or not clear in literature.

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the safe and easy elimination and detoxification of the drug substance (balanced clearance, inactive metabolites).

As table II shows, almost all of the 13 β-blockers considered fulfil the practical experimental conditions, bioanalytical methodology (crit. 1) (see table II, column 1) and the correlation with effects (crit. 8). Furthermore most β-blockers are applicable once daily (crit. 2) due to the long duration of action, they have a good absorption (crit. 4) with the exception of acebutolol, atenolol and nadolol, and they have linear pharmacokinetics (crit. 9) in the whole dosage range with the exception of alprenolol and propranolol. However, most of the β-blockers fall short of a complete oral bioavailability (crit. 6) due to a large first-pass effect (crit. 5). This is one of the reasons for the high daily dosages (crit. 3) and the not well-predictable steady-state plasma levels (crit. 10). Most β-blockers have small protein bindings (crit. 7) except propranolol and alprenolol. Only timolol, pindolol, acebutolol and sotalol have a somewhat balanced clearance (crit. 12) (4); all the other β-blockers are either cleared exclusively by the kidney or the liver. The formed metabolites are mainly inactive (crit. 11). In summarizing table II, only pindolol fulfils all the desired 12 criteria, whereas propranolol and alprenolol only reach three positive points in this scaling.

Origin of Differences

Chemically, the β-adrenoceptor-blocking agents are similar by having in all but a few cases an isopropylaminopropoxy side chain (a major element for their pharmacological and therapeutic activity) and an aromatic group varying in structure for the different drugs. This latter group, which could be called the modulator of the pharmacological activity, also determines the pharmacokinetic properties of these drugs. Figure 1 demonstrates how the aromatic ring of the β-blocker leads to different lipophilicities of the drug molecules. Pharmacokinetically this influences the protein binding, the hepatic extraction ratio and the volume of distribution. This is illustrated by the observation that the most lipophilic β-blockers (like alprenolol and propranolol) have a strong protein binding, a large hepatic extraction ratio, are completely metabolized in the liver and show shorter half-lives; whereas those of lower lipophilicity (like practolol or sotalol) are mainly excreted via the kidney and have longer half-lives of elimination. The volume of distribution also increases with higher lipophilicity of the drug (1, 5). From all these factors collected in figure 1, the hepatic extraction ratio mostly affects the relevant pharmacokinetics. A high extraction

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Protein binding

Blood flow-limited kinetics

↓ Saturation effects

Nonlinearities
 Aromatic ring of α -blocker
 ↓
 Lipophilicity
 ↓
 Hepatic extraction ratio
 ↓
 First-pass effect
 ↓ Oral bioavailability
 Intersubject variability
 Volume of distribution
 Balance of clearance
 ↓ Dosage in disease states

Fig. 1. Chemical differences lead to pharmacokinetic differences of the β -adreno-ceptor-blocking agents due to different lipophilicities.

ratio in the liver leads ultimately to liver blood-flow-limited kinetics (which causes pharmacokinetic saturation effects and nonlinearities) and to a high first-pass effect (which reduces oral bioavailability and causes large intersubject variability in plasma levels and effects). Furthermore, the hepatic extraction ratio influences the pathway of clearance and therefore the dosage regimen in liver or kidney insufficiency.

First-Pass Effect and Bioavailability

As illustrated in tables I and II, all β -blockers (with the exception of acebutolol, atenolol and nadolol) are absorbed completely. However, the extent of their bioavailability differs strongly due to the variations in the extent of pre-systemic metabolism by the liver upon portal transport (first-pass effect). Practolol, pindolol and sotalol have negligible first-pass effects as compared to propranolol (70%), alprenolol (90%), metoprolol (50%), oxprenolol (30–50%) (1, 4) and labetalol (60%) (6).

Figure 2 illustrates how the first-pass effect can be determined as difference between the totally absorbed minus the bioavailable fraction of the dose. After intravenous and peroral administration of ^{14}C -labeled pindolol to man the plasma levels and the urinary excretions were measured. Both the total ^{14}C -radioactivity (representing unchanged pindolol and its metabolites) and the unchanged drug alone were determined and compared for the two routes of administration. Based on the plasma levels and the cumulative urinary excretion

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Fig. 2. Determination of the absorption, the absolute oral bioavailability and the first-pass effect of pindolol in man (7). After oral and intravenous administration of ^{14}C -labeled pindolol the plasma levels and urinary excretions were determined. $\bullet$ = ^{14}C -radioactivities = parent drug + metabolites; $\square$ = parent drug alone.

of ^{14}C -radioactivity, which are quite similar after oral and intravenous administration, the complete absorption of pindolol in man could be concluded. The lower curves in figure 2 represent the parent drug. Their comparison after oral and intravenous administration indicated an 87% absolute bioavailability. Therefore, pindolol has a small first-pass effect of about 13% in man (7). Similar experiments in the rat and the dog (8) yielded 40 and 45% first-pass effect. Since the metabolism of pindolol is much more extensive in animals than in man, it could be

proven that the first-pass effect of β -blockers is directly correlated to the hepatic extraction ratio (4, 8).

Two parameters, the hepatic extraction ratio and the hepatic blood flow, contribute to the unpredictability of plasma levels in the β -blockers with high hepatic clearance in the following ways.

First, the hepatic extraction and metabolism of a β -blocker may be saturated by an increase in dose leading to a more than proportional increase in plasma concentration. This phenomenon is important for propranolol (9) and alprenolol (10), whereas plasma pindolol levels rise in proportion to the oral dose, the bioavailability being independent of dose (7, 11) (see fig. 3).

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600

Fig. 3. Linear relationship between plasma concentrations ($\pm$ SEM) of pindolol (AUC : area under the curve) and different dosages after single oral administrations (7).

1.5 μ g

E

S 1.3

10

ω

S 1.2

3 1.1 >

< TJ

o S 1.0

First-pass effect of β -blockers correlates with: F5D (AUC)

Increase of AUC (bioavailability) with food

-0.4

Inter-subject variability of AUC (plasma levels)

0.2

1

Pindolol

f r-

4 1

Metoprolol Propranolol T

10 20 30 40 50 60 70 First-pass effect, %

Fig. 4. Correlation of the first-pass effect with the intersubject variability of plasma levels and with the increase of the plasma levels by simultaneous food intake demonstrated on pindolol (14), metoprolol (15) and propranolol (15).

The influence of liver blood flow on hepatic drug clearance has been described, in a fundamental paper by Wilkinson and Shand (12), as have been the pharmacokinetics in disease states modifying body perfusion (13). A reduction in hepatic blood flow (with advancing age, in cardiac insufficiency or liver cirrhosis or as a consequence of chronic β -blocker administration) will reduce

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100	80	60	40	20	0
0	20	40	60	80	100

mm t t tt ttt

Alprenolol Timolol Pindolol Acebutolol Practolol

Propranolol Sotalol Atenolol

Metoprolol Nadolol

Oxprenolol

Labetalol

Penbutolol

Fig. 5. Balance of clearance: Clearance of 13 β -adrenoceptor-blocking agents by the liver and/or the kidney.

hepatic metabolization and, therefore, produce higher plasma levels and longer half-lives in β -blockers with intense hepatic clearance. Figure 4 demonstrates in the examples pindolol (14), metoprolol (15) and propranolol (15) how the first-pass effect correlates with the intersubject variability of the plasma levels and with the increase of the bioavailability by simultaneous food intake.

The disadvantage of a strong first-pass effect is, therefore, not only the lower availability after peroral administration which can be compensated by higher dosage, but also the resulting unpredictable larger biological, individual variation in the plasma levels and drug response and the difficulty in ascertaining a desired steady-state level.

Clearance

There are wide differences in the 13 β -adrenoceptor-blocking agents as to how they are cleared (fig. 5). Practolol, atenolol and nadolol, for instance, are completely cleared by the kidneys. In kidney impairment the dosage has to be reduced, otherwise a considerable drug accumulation in the organism might occur due to the diminished elimination half-lives (16, 17). On the other hand (fig. 5), the β -blockers alprenolol, propranolol, metoprolol, oxprenolol, labetalol and penbutolol are almost entirely eliminated by hepatic metabolism. In this case, it could be shown that the clearance decreased with increasing impairment of the liver function (18).

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Table III. Increase of elimination half-lives of some β -blockers in patients with renal impairment-

With renal impairment	Normal subjects	Factor of increase
Practolol	60–100 h	5–13 h 6.6
Sotalol 42 h	7h 6	
Atenolol	22 h 5 h	4.4
Acebutolol	12 h 3 h	4
Pindolol	5h 3–4 h	1.4

Table III demonstrates the increase of the elimination half-lives in renal impairment. As expected the drugs are affected according to their degree of renal clearance in the order: practolol > sotalol > atenolol > acebutolol > pindolol. Pindolol and timolol take an intermediate position (fig. 5).

Since 60% of pindolol is cleared by the liver and 40% by the kidney, there should be no appreciable change in pindolol elimination in patients with liver or kidney function failure, unlike the case with propranolol in liver disease or practolol in renal disease.

Ohnhaus (19) found no change in the elimination rate constant or half-life of unchanged pindolol in patients with impaired renal function and reduced creatinine clearance. This suggested an increase in the hepatic metabolism of the substance when renal impairment is present. This was

subsequently confirmed (20) when a greatly increased rate of metabolite formation in anuric patients was demonstrated with accumulation of inactive metabolites but not of unchanged drug in the plasma. Øie and Levy (21) found a positive correlation between the renal clearance of pindolol and the creatinine clearance, but again no statistically significant correlation ($n \approx 24$ patients) was found between the important over-all clearance of pindolol and the creatinine clearance. Lavène et al. (22) found decreased renal clearance of pindolol in kidney insufficiency; however, a reduced oral bioavailability in such patients was suggested, as it is commonly observed in chronic renal failure. A recent study of Galeazzi (unpublished) showed that in renal impairment both the plasma levels of pindolol and the exercise-induced tachycardia were affected only in a minimal and not relevant manner. At the very worst, the usual elimination half-life of pindolol is prolonged by a factor 1.4 (23) in patients with impaired renal function, as against a factor 4 for atenolol and acebutolol, 6 for sotalol and about 7 for practolol

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Fig. 6. Comparison of pindolol (parent drug) plasma concentrations (mean $\pm$ SEM) in rhesus monkeys after 5 years of chronic treatment (*, $n = 7$) and after the first treatment in a control group ($\cdot$, $n = 8$) (31). F values are dose- and weight-normalized concentrations: $F \times \text{dose} \left(\frac{\text{mg}}{\text{kg}} \right) = \text{concentration} \left(\frac{\mu\text{g}}{\text{g}} \right)$ in plasma.

(table III). Timolol (24) has also a balanced clearance and its plasma levels are also not greatly influenced in renal impairment.

Ohnhaus et al. (25) found no correlation between antipyrine clearance – a measure of hepatic metabolic activity – and the overall elimination rate constant or metabolic clearance of intravenous pindolol in patients with hepatic disease but normal renal function, except in patients with very low antipyrine clearance (below 10 ml/min). Therefore, no modification of pindolol dosage appears necessary in patients with partial kidney or liver insufficiency.

Interestingly enough, propranolol, which is cleared mainly by hepatic metabolism, has shown much higher plasma levels in patients with renal impairment or terminal uremia (26, 27). This has been related to a change in the first-pass effect or in the volume of distribution in this type of patient.

Predictability of Plasma Levels

β -Blockers are drugs which will be used in long-term treatment and the question of their long-term efficacy and safety is of interest. Pharmacokinetic data in this respect are only available for a few β -blockers. Two of the best studied compounds which have been on the market for a considerable period of time, propranolol and pindolol, show interesting differences in their kinetics

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Fig. 7. Comparison of pindolol plasma concentrations (^{14}C -radioactivities, parent drug plus metabolites, mean $\pm$ SEM) in rhesus monkeys after 5 years of chronic treatment (*, $n = 7$) and after the first treatment in a control group ($\cdot$, $n = 8$) (31). F values are dose- and weight-normalized concentrations: $F \times \text{dose} \left(\frac{\text{mg}}{\text{kg}} \right) = \text{concentration} \left(\frac{\mu\text{g}}{\text{g}} \right)$ in plasma.

after multiple-dose treatment: the plasma elimination half-life of pindolol did not change after multiple dosing (28) as had been found previously for propranolol (29). In addition there was a 60% increase in the amount of propranolol reaching the systemic circulation at steady state compared to that after a single dose (29) due to saturation of the hepatic extraction process. For metoprolol, it has been reported (30) that elimination half-life was almost the same after single

dosing or long-term administration, but there was some cumulation observed after repeated administration. The predictability of pindolol plasma levels could also be demonstrated in the rhesus monkey (31). After chronically treating rhesus monkeys for 5 years with high doses of pindolol, there were no relevant nor significant differences in the absorption, distribution, metabolism and excretion of pindolol in comparison to the first treatment of a control group. Figure 6 shows the very similar plasma levels of unchanged pindolol in the two groups of monkeys and figure 7 demonstrates a similar finding for the plasma concentrations of ¹⁴C-radioactivity (parent drug plus metabolites).

Conclusion

The 13 β -adrenoceptor-blocking drugs vary widely in their pharmacokinetic profile. Pindolol has ideal pharmacokinetic properties (table II) which yield

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Table IV. Pharmacokinetically based advantages of pindolol in therapy

Pharmacokinetic facts

Therapeutical advantages

High bioavailability

Low first-pass effect

Moderate metabolism

Low protein binding

Balanced clearance by the kidney and the liver

Partly compensating factors in liver or kidney insufficiency

Low daily dosage

No saturation effects

Small variations in plasma levels and effects

No accumulation of pindolol in patients with renal or hepatic impairment (not critical in dosing) some therapeutical advantages (4). A low daily dosage is possible because of the high bioavailability, low first-pass effect, the moderate metabolism (fig. 2) and the potency of pindolol. Due to the low first-pass effect and the low daily dosage there are no saturation effects, and the low first-pass effect, moderate metabolism and low protein binding mean that with pindolol there are only small variations in plasma levels and drug effects. Finally, due to the balanced clearance and probably some compensating factors, there is unlikely to be any accumulation of pindolol in patients with renal or hepatic impairment (see table IV).

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