Multimorbidity and polypharmacy: Which betablocker to use in relation to the pharmacokinetic profile and interaction potential

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Abstract

Betablockers still represent widely prescribed drugs as they cover a wide spectrum of cardiovascular indications. Obviously, it is not trivial which betablocker to choose as they differ both with regard to their pharmacodynamic (e. g. selective vs. nonselective, beta *vs.* beta + alpha blocking activities) and pharmacokinetic profiles. Latter is largely governed by the metabolic properties, and, thus, their excretion route (renal or biliary route in unchanged or metabolized form). In the elderly population, the stability of plasma concentrations is particularly essential as this population has smaller compensatory tolerance to concentration variations than younger patients. The interaction potential of betablockers with regard to drug-drug, gene polymorphism-drug, excreting organ-drug interactions varies widely between individual substances. Compounds predominantly metabolized by polymorphic cytochromes such as CYP2D6 are affected by the metabolizer status and competing compounds utilizing the same metabolic pathways can strongly influence plasma levels (examples metoprolol [CAS 37350-58-6], carvedilol [CAS 72956-09-3]). On the other hand, metabolically stable compounds which are predominantly excreted renally may be unfavourable as their plasma concentrations largely depend on renal function which may be blunted in elderly patients. The prototype of this category, atenolol (CAS 29122-68-7), has been associated with inferior results in mortality trials in hypertension treatment.

Thus, a favourable compound should be partially stable in regard to metabolism to depend less on drug-drug and gene-drug interactions, but also utilize more than one route of excretion, meaning both the direct renal and the metabolic routes. The prototype for this type of betablocker is bisoprolol (CAS 66722-44-9).

Key words

- **Betablockers**
- **Interactions**
- **Multimorbidity**
- **Polypharmacy**

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1. Introduction and scope of the clinical problem

Drug therapy is the most relevant therapeutic intervention in medicine; elderly patients often suffer from multiple diseases (multimorbidity) and this is reflected by multiple drug treatments (polypharmacy). Kaufmann *et al.* [1] showed that patients aged 65 and above take >5 drugs in 44 % (male) and 57 % (female) of cases and >10 drugs in 12 % of cases. It is obvious that drug therapies of 10 and more drugs are unpredictable, expensive and can cause more harm than good, given that up to 100 000 deaths in the U.S. annually are attributable to drug use [2].

The demographic revolution with a rapid growth of the elderly population will sharply increase this problem: by 2030, elderly people aged 80 and above will represent 6–8 % of the French, Spanish, British and German, and even 12 % of the Japanese populations, comparing to only 4–5 % in 2010 [3].

Among those drugs, betablockers still represent a widely used group of drugs; in Germany, a generic preparation of metoprolol ranged on place 9 of a list of most-prescribed medications in 2007 [4].

Betablocking agents are essential components of pharmacotherapy in all major cardiovascular diseases such as hypertension, coronary heart disease, post-

myocardial infarction prevention, arrhythmias or – relatively recent – heart failure [5]. Betablocking agents and diuretics represented the first "modern" antihypertensive drugs, with propranolol (CAS 525-66-6) being the first clinically used prototype introduced as early as 1964. Their spectrum of indications does not only include those cardiovascular conditions, but also migraine prophylaxis, treatment of portal hypertension, tremor in Parkinson syndromes, wide-angle glaucoma (local therapy) and others.

Though the life-prolonging aspects of betablocker use especially in the post-myocardial infarction situation had been recognized very early, the scope of interest for this group of drugs receded in the 80ies and early 90ies of the past century. It was only revitalized when the first studies showed the large clinical benefit resulting from its use in heart failure (e.g. [6]). Along with this, interest in differentiation criteria for the various classes of betablocker was renewed which is one of the most heterogenous groups of cardiovascular drugs available today. Betablockers expose at least 3 very important dimensions of pharmacological profiling.

1. Heart rate modification remains the main determinant of anti-ischemic action by, for example, betablockers, discriminating compounds with intrinsic sympathomimetic activity (ISA) from those without ISA. Only the latter reduce both heart rate and postmyocardial infarction mortality [7, 8].

2. Receptor specificity comprises cardioselectivity which means the predominant affinity towards beta-1-adrenergic receptors which particularly reside in the heart, and additional receptor effects, especially alpha-adrenergic or nitric oxide-mediated effects [8].

3. Pharmacokinetic variability of a compound in different clinical situations mainly reflects absorption, distribution, metabolic stability and excretion routes for a particular compound, with latter two components being of particular importance in this context.

It is obvious that 1–3 are independent of each other and, thus, the profile of one of the about 25 + different marketed betablockers could be very different from that of another compound.

Compound profiling, therefore, is of paramount importance for the tailored treatment of an individual patient nowadays called "personalized medicine".

This review is focused on the pharmacokinetic differences of frequently used betablockers which are of particular importance for the multimorbidity/polypharmacy situation as drug-disease, drug-drug and gene-drug interactions are particularly relevant especially for elderly drug users.

Drug-drug interactions involving betablockers were already described in the 1980s [9], and regularly thereafter (e.g. [10, 11]). At that time, many aspects of genetic variations affecting metabolism had not been fully recognized; in consequence, they have not been reflected in the clinical development of drugs, including betablockers, and in the regulatory processes.

Nowadays, gene polymorphism is a catchword; metabolic enzyme polymorphisms are regularly considered in current drug development if relevant. Given the clinical importance of betablockers, older compounds lack such data from their original development, but need to be re-assessed in the light of newer investigations and clinical trials. By this, they should be re-positioned especially in the plot of polypharmacy, by considering the dependence of efficacy and safety aspects on polymorphic metabolic enzymes and related drug-drug interactions.

This is the main goal of this review. Other dimensions (see above, 1 and 2) are not discussed in this review, but are, of course, very important for tailored betablocker therapy as well.

2. Pharmacokinetic profiling of betablockers

The pharmacokinetic data of any compound are characterized by basic figures, mainly absorption rate, half-life, volume of distribution and dosing regimens depending on the disease to be treated. This review does not aim at the collection of these numbers which can be easily found elsewhere. If the user applies the recommended dose at the recommended dosing intervals, e.g. the half-life should be correctly reflected.

However, the interaction potential of a drug with other drugs, diseases or genes is more difficult to cover as it is potentially influenced by a multitude of independent, partly unknown factors and, thus, hardly predictable in many instances. These therapeutically relevant conditions are the topic of this review.

3. Metabolic stability and drug-gene interactions

Like all drugs, betablockers can be categorized in regard to their metabolic stability into three groups (Table 1):

1. extensively metabolized
2. not significantly metabolized
3. partially metabolized

When looking at the most commonly used betablockers, extensively metabolized betablockers are metoprolol (CAS 37350-58-6), carvedilol (CAS 72956-09-3), nebivolol (CAS 99200-09-6) and esmolol (CAS 103598-03-4). Propranolol (CAS 525-66-6) belongs to this class though it is no longer used at large and, thus, not further discussed in this review.

Partially metabolized is bisoprolol (CAS 66722-44-9), metabolically stable are atenolol (CAS 29122-68-7), celiprolol (CAS 56980-93-9) and sotalol (CAS 3930-20-9).

Metabolism of betablockers predominantly occurs through the cytochrome P450 enzyme variant 2D6. This applies to metoprolol, carvedilol [12] and nebivolol [13], while esmolol as a very short acting betablocker is metabolized by erythrocyte esterases [14] which will not further be discussed here as this compound is not used in long-term treatment.

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Table 1: Pharmacokinetic categories of betablockers in regard to metabolic stability, and the related prototype compounds

Pharmacokinetic category	Prototype	Main route of excretion/metabolism	Advantage(s)	Disadvantage(s)
Metabolized	Metoprolol	Metabolized by CYP450 2D6	PK independent of kidney function	Interaction potential: drug-drug (pharmacokinetic), drug-gene, drug-organ (liver)
Not metabolized	Atenolol	Renal excretion of unchanged compound	PK independent of liver function	Interaction potential: drug-organ (kidney), kidney function often impaired in elderly patients, unrecognized, or impaired by concomitant drugs
Partially metabolized	Bisoprolol	Drug both metabolized and excreted as unchanged compound	PK not dependent on one excretory organ only, stable pharmacokinetics in mild to moderate excretory organ impairment and polypharmacy situations with particular relevance to the growing elderly population	

Bisoprolol is partially metabolized (about 50 %); this is not dominantly due to CYP450 2D6 (only 5 % of the compound metabolism), but to the variant CYP450 3A4 [12].

While stereoselective metabolism of the R(+) and S(–) enantiomers resulting in enantiomeric imbalances by enzyme blockade could be of relevance e. g. for carvedilol [15], its general clinical importance seems to be limited in comparison to other implications of metabolic drug elimination to be further discussed here.

Drug metabolism as such has two essential bearings with regard to the polypharmacy/multimorbidity situation of many elderly patients:

a) the metabolizing enzyme may be utilized by more than one of the many drugs which could cause lowered drug metabolism resulting in higher plasma levels (competition and/or inhibition at the enzyme level) or its activity may be induced by other drugs resulting in lower plasma levels (prototype CYP 3A4 induction by rifampicin)
b) the activity of the enzyme is genetically determined and some patients have lower, some have higher than average activities; the low activity situation can be mimicked by organ (mainly liver) damage, e. g. in liver cirrhosis.

Unfortunately, CYP450 2D6 is relevant for both mechanisms of altered plasma concentrations which in the case of elevations may lead to increased rates of side effects, in case of lower concentrations to treatment failures.

This enzyme is the CYP variant for which the concept of "poor", "extensive" and "ultrarapid" metabolizer (PM, EM, UM) was originally developed [16]. The prevalence of the PM-status is 7 % for Caucasians while in Asia it is only 1 % [17, 18]. The UM-type is present in 3–5 % of Caucasians, but in 15–20 % of Asian populations [19].

Among the β-blockers discussed here, metabolism of metoprolol is predominantly dependent on the CYP2D6 enzyme, with 70–80 % of its metabolism utilizing this pathway. The allelic polymorphisms of 2D6 result in major differences in metoprolol plasma levels. The peak plasma concentration of metoprolol is threefold higher, and the area under the plasma concentration time curve (AUC) is sixfold greater in PMs than in EMs [20]. Wuttke *et al.* showed that PM patients have a fivefold higher risk of developing adverse effects during metoprolol treatment than patients who are not PMs [21]. In another study from the same group, it was shown that the pharmacokinetic impact of CYP2D6 alleles persisted in long-term treatment for 12.6 months [22]. However, these were retrospective studies with limited sample sizes. Prospective studies with larger samples did not confirm these results. Specifically, although the expected effects of CYP2D6 genotype on pharmacokinetics of metoprolol were observed, rates of efficacy or adverse effects were not significantly different between the poor metabolizer and non–poor metabolizer groups in those prospective studies [23, 24]; for review see [25].

Though these studies are yet inconclusive it is hard to reconcile that sixfold differences in plasma concentrations of a betablocker should not result in increased adverse reactions, at least not in the frail elderly patients facing polypharmacy problems. However, systematic studies in this population are not available.

The other important aspect which may add to the genetic variance situation is drug-drug interaction which may be anticipated for drugs utilizing the same enzyme for metabolism.

Important drugs in this context are fluoxetine, paroxetine, sertraline, cimetidine, protease inhibitors, amiodarone, propafenone, flecainide/encainide, tricyclic antidepressants (e. g. amytriptyline), neuroleptics (e. g. risperidone, haloperidol) and codeine (list incomplete).

There have been reports on adverse effects – amongst others – for the interaction of metoprolol with fluoxetine

[10], paroxetine [11] and propafenone [9]. This shows that interactions may not only be related to other cardiovascular, but completely unrelated drug groups, especially CNS-drugs.

More recently, it was shown that in CYP2D6 EM healthy subjects, dronedarone increased plasma concentrations of metoprolol in a dose-dependent manner and induced an additional dose-related negative inotropic effect [26]. On the other hand, UM may not benefit from effective betablockade by metoprolol in acute myocardial infarction [27].

The other CYP variant which is relevant for e.g. the partial metabolism of bisoprolol [28] is CYP450 3A4. This is the metabolizing enzyme for about 50% of all metabolized drugs; thus, drug-drug interactions are theoretically possible for almost all patients on polypharmacy schemes. However, given that the strong inhibitor of CYP 3A4, cimetidine, did not have an effect on the elimination half-life of bisoprolol, this particular interaction potential of bisoprolol seems to be of small relevance. The CYP 3A4 inducer, rifampicin, led to a 30% decrease of the elimination half-life [29].

These data support the assumption that drug-drug interactions at the pharmacokinetic level do not play a relevant role in the clinical profile of bisoprolol, and indeed observations on interactions with other drugs, especially in the cardiovascular field, seem to predominantly reflect pharmacodynamic interactions, e.g. increased negative inotropy in addition to calcium antagonists [30].

Nozawa *et al.* [31] compared plasma levels of metoprolol and bisoprolol and pharmacological responses of patients to adrenergic stimulation in relation to CYP4502D6 polymorphisms. They found that CYP2D6 genotypes significantly affect circadian variations of beta-adrenergic blockade induced by chronic treatment with metoprolol. In contrast, bisoprolol induced a relatively constant beta-adrenergic inhibition independent of the CYP2D6 genotype.

In this context, it is important to note that Asian populations do not only comprise 15–20% of UM for CYP2D6 [19], but also carry a low activity allele, CYP2D6*10 [31], in 20% of cases. This finding was corroborated in two additional studies for a Chinese [32] and a Japanese population [33].

This may explain why Asian populations are relatively sensitive to betablockade in terms of heart rate reduction; adverse effects of metoprolol in the POISE-study in which this betablocker was given to 8351 patients perioperatively at doses of up to 400 mg/day may be related to the CYP2D6*10 variant as many patients were recruited in China [34].

In addition to metabolic processes drug-transporters and drug-drug interactions at this level are increasingly seen to be important in the pharmacokinetics of drugs. The main transporter is P-glycoprotein though many other transport proteins have been identified. Bachmakov *et al.* [35] provided *in vitro* evidence that P-glycoprotein can be influenced by propranolol and carvedilol in terms of relevant interactions with digoxin or cyclosporine, whereas it may play a role in bisoprolol and cyclosporine disposition. Unlike the characterization of metabolic processes, the characterization of the main betablockers in regard to transport proteins is not far developed.

4. Route of excretion

In principle, a drug can leave the body only through the kidneys and bile/feces (gases excepted), either requiring prior metabolic transformation or not.

Atenolol is the prototype of a widely used betablocker which is almost entirely excreted through the kidneys in its unchanged form. It is hydrophilic and thus does not readily cross membranes required e.g. for first-pass metabolism in the liver. As such, pharmacokinetic drug-drug interactions are unlikely to occur, but its excretion critically depends on kidney function. The latter, however, is decreasing with age (down by up to 50% in two thirds of all elderly patients [36]), and – may be even worse – can be negatively impacted by a variety of other drugs. These would be pharmacodynamic drug-drug interactions as opposed to pharmacokinetic drug-drug interactions described above. Drugs predisposing to aggravation of renal failure in the elderly are nonsteroidal anti-inflammatory drugs (NSAIDs), inhibitors of the renin-angiotensin-system (ACE-inhibitors, angiotensin-receptor antagonists), spironolactone, aminoglycoside antibiotics and others. These effects can be further potentiated by malnutrition, concurrent infections, diarrhea and inadequate fluid intake. It is obvious that atenolol dosage needs to be adjusted according to kidney function [37]. The latter could be easily obtained by estimation, e.g. by the use of the Cockroft-Gault formula [38], but adherence to this approach is not sufficient in daily practice, and impaired function of excreting organs is a risk factor for adverse drug effects in the aged [39]. Atenolol (and sotalol) need to be revisited in the treatment of the elderly as the exclusive renal excretion is potentially dangerous.

Up to now, there is an ongoing discussion about the inferiority of this particular betablocker in the LIFE trial on hypertension treatment in the elderly in comparison to losartan [40]. An inferior result was also seen in the ASCOT-BPLA trial, here tested against amlodipine [41]. The unsolved question is whether those results just reflect the disadvantage of atenolol, e.g. because of its critical dependence on a fragile excretion organ, the kidney, or whether these results should be generalized to all betablockers. In fact, atenolol (or betablockers in general?) are no longer seen as a first-line treatment of uncomplicated arterial hypertension in the elderly (for review see [42]). In this context it is important to note that blood pressure reduction by bisoprolol was equi-effective in younger and elderly patients whereas atenolol was less effective in the elderly [43]. This may explain

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the somewhat smaller blood pressure reduction in the ASCOT-BPLA trial (blood pressure in amlodipine *vs.* atenolol group: SBP –2.7 mm Hg, DBP –1.9 mm Hg) [41] by atenolol than by amlodipine, and another betablocker may have been more appropriate in this study.

At present, however, this problem cannot be tackled as the other betablockers have not been widely used in head-to-head studies on hypertension treatment. In a recent Cochrane review on betablocker treatment of hypertension, 75 % of all data for betablockers were atenolol data [44]. On the other hand, it is also unclear why registry data comparing mortality of heart failure patients did *not* show inferiority of atenolol versus other betablockers [45].

Bisoprolol is the prototype of a betablocker which utilizes two routes of elimination: it is partially metabolized (50 %, see above), and the metabolites are renally cleared along with the unchanged compound (50 %). This balanced excretion thus involves both main excretory organs, *viz.* the liver and the kidneys.

Thus, in case of failure of one excretory organ slightly higher plasma levels will drive the increased utilization of the other path; or in other words, if the metabolic process is impaired (e. g. in hepatic failure) more unchanged compound will be renally excreted and if the renal function is impaired more compound will be metabolized (accumulation of the metabolite which needs to be renally cleared as well is no clinical problem as it is inactive). This is reflected by the fact that even in severe renal or hepatic failure, the maximum increase of bisoprolol plasma levels was only twofold [46,47]. The clinical consequence is reflected in the dosing recommendations: no dose adjustment is necessary in mild to moderate renal or hepatic failure; in severe cases the maximum dose of 20 mg should be reduced to 10 mg. Thus, it is fair to say that bisoprolol is the only betablocker for which neither renal nor hepatic failure of any degree has relevant impact on dosing schemes.

This pharmacokinetic stability is also reflected by the absence of a sex- or age dependency of plasma levels [48]. In this regard, bisoprolol is unique.

Celiprolol has a dual excretion path through the kidneys and the bile in the unchanged form, but exposes ISA and is, thus, not in line with the goals of cardiovascular protection through heart rate reduction (see above). Talinolol is also metabolically stable and excreted through the kidneys (60 %) and feces (40 %), but lacks data in large mortality trials. Results from the CITAS trial have not been published though it should have been completed in 2000 [49].

The clinical importance of stable pharmacokinetics in elderly patients on polypharmacy schemes, in patients with deterioration of excretory organ functions has not been systematically and comparatively studied for bisoprolol or other betablockers. In a small study, bisoprolol seemed equally effective and safe in young and elderly patients [50], which is in line with its pharmacokinetic stability.

Direct head-to-head comparisons of different betablockers are yet rare or even absent, as for the elderly population; the outcome of the ongoing CIBIS-ELD trial [51] comparing bisoprolol and carvedilol in elderly heart failure patients may help to improve this situation.

Therefore, so far any conclusion drawn from the considerations described here is extrapolated and requires confirmation in clinical studies.

5. Conclusions

Patients aged 65 and above take > 5 drugs in 44 % (male) and 57 % (female) of cases and > 10 drugs in 12 % of cases with cardiovascular diseases among the leading diagnoses. Drug therapy in these patients thus is typically multiple, and polypharmacy problems are common. Drug therapies of 10 and more drugs are unpredictable, and seem to cause more harm than good, given that up to 100 000 deaths in the U.S. annually are attributed to medications.

Betablockers still represent widely prescribed drugs in these patients as they cover a wide spectrum of indications: coronary heart disease, arrhythmias (e. g. atrial fibrillation), heart failure, hypertension, just to name a few. There are 25 + different betablockers on the market, and thus, obviously, it is not trivial which betablocker to choose as they differ both with regard to their pharmacodynamic (e. g. selective vs. nonselective, beta *vs.* beta+ alpha blocking activities) and pharmacokinetic profile. The latter is largely governed by the metabolic properties, and, thus, their excretion route (renal or biliary route in unchanged or metabolized form). In the elderly population, the stability of plasma concentrations is particularly essential as this population has smaller compensatory tolerance to concentration variation than younger patients. The interaction potential of betablockers with regard to drug-drug, gene polymorphism-drug, excreting organ-drug interactions varies widely between individual substances. Compounds predominantly metabolized by polymorphic cytochromes such as the variant CYP2D6 are affected by the metabolizer status, and competing compounds utilizing the same metabolic pathways can strongly influence plasma levels (examples metoprolol, propranolol). The drug-drug interaction problem is aggravated in the polypharmacy situation of many elderly patients. On the other hand, metabolically stable compounds which are predominantly excreted through the kidneys may be unfavourable as their plasma concentrations largely depend on renal function which may be blunted in elderly patients by age-related deterioration or concomitant drugs. Even worse, this remains often undetected. The prototype of this category, atenolol, has been associated with inferior results in mortality trials in hypertension treatment such as LIFE, and it is still unclear how this may be generalized to all betablockers.

Thus, a favourable compound should be at least partly stable in regard to metabolism to be largely de-

void of drug-drug and gene-drug interactions, but also utilize more than one route of excretion, meaning both the direct renal and the metabolic routes. The prototype for this type of betablocker is bisoprolol.

Small clinical trials have pointed to the clinical relevance of these aspects, though further investigations are necessary to support the practical utility of these properties.

Competing interests

The author was employed by AstraZeneca R&D, Mölndal, Sweden, as director of discovery medicine (= translational medicine) from 2003–2006, while on sabbatical leave from his professorship at the University of Heidelberg. After return to this position in January 2007, he received lecturing and consulting fees from Sanofi-Aventis, Daiichi-Sankyo, Novartis, Takeda, Roche, Pfizer, Bristol-Myers, Lilly and Novo-Nordisk.

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