Kidney Medicine

Should We Use Dialyzable β-Blockers in Hemodialysis?

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Dialyzability is a pharmacokinetic parameter that reflects the efficiency of drug withdrawal from the circulation by the filter of hemodialysis.[1] Whether a drug is extensively cleared during hemodialysis is determined by its physicochemical characteristics and its overall pharmacokinetic profile.[1] β-Adrenergic receptor blockers (β-blockers) are among the most commonly prescribed antihypertensive medications among patients receiving hemodialysis.[2] The β-blocker category contains agents with considerably variable dialyzability. For example, hydrophilic β-blockers are more susceptible to filtering by the hemodialysis membrane than β-blockers with high lipid solubility.[1,3] The use of highly dialyzable β-blockers may result in abrupt losses of the drug during the hemodialysis procedure and in subtherapeutic plasma concentrations over the interdialytic interval.[4] Accordingly, it can be hypothesized that the limited therapeutic efficiency of highly dialyzable β-blockers may thereafter aggravate the risk of adverse cardiovascular events and all-cause death.

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In this issue of *Kidney Medicine*, Tella et al[5] performed a systematic review of the literature aiming to identify studies comparing the safety and efficacy of highly dialyzable and poorly dialyzable β-blockers in patients receiving hemodialysis. Of the 78 potentially relevant reports retrieved, only 4 studies met the prespecified inclusion/exclusion criteria, and, unfortunately, the literature search failed to identify any randomized controlled trial that provided a head-to-head comparison between β-blockers with different degrees of dialyzability. Taking into consideration that all 4 eligible studies followed a retrospective observational design, it is not surprising that method quality assessment graded these studies as having an overall "high" risk of bias.[5] When risk ratios from fully adjusted Cox regression models of each individual study were inserted in quantitative data synthesis, there was no significant difference between highly dialyzable and poorly dialyzable β-blockers in all-cause death risk (hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.81-1.08).[5] Unlike the accumulated concerns around the cardiovascular safety of highly dialyzable β-blockers, their use was associated with 12% lower risk of adverse cardiovascular events (HR, 0.88; 95% CI, 0.83-0.93).[5]

The classification of β-blockers into highly or poorly dialyzable is the first issue that warrants careful examination. Of the 4 studies included in this meta-analysis,[6-9] the only study that associated the use of highly dialyzable β-blockers with harm was a propensity-matched, population-based, retrospective analysis incorporating data from linked health care databases from Ontario, Canada.[8] In the high-dialyzability group, 3,294 patients receiving hemodialysis were new users of atenolol, acebutolol, or metoprolol. The low-dialyzability group included 3,294 patients receiving hemodialysis who initiated therapy with bisoprolol or propranolol. Initiation of a highly dialyzable versus a poorly dialyzable β-blocker was associated with 40% excess risk of all-cause mortality over a follow-up of 180 days.[8] The classification of bisoprolol as a poorly dialyzable β-blocker in this study was based on physicochemical characteristics of this agent and on the evidence from earlier pharmacokinetic studies that were conducted before the implementation of high-efficiency hemodialysis with high-flux membranes.[10]

In sharp contrast, a recent multiway, open-label, crossover trial investigating the pharmacokinetic properties of 4 commonly prescribed β-blockers in 8 patients receiving high-flux hemodialysis unexpectedly showed that bisoprolol also exhibits a substantial dialytic clearance.[11] Taking into consideration that >80% of patients in the low-dialyzability group were being treated with bisoprolol, a β-blocker that was proven to be highly dialyzable in a subsequent pharmacokinetic study, the analysis of Weir et al[8] is not informative with respect to the potential effect of β-blocker dialyzability on all-cause mortality. The between-group difference in clinical outcomes that was observed in this study is probably due to other contributing factors.

Accordingly, in their report, Tella et al[5] performed a sensitivity analysis addressing the issue of misclassification of bisoprolol as a poorly dialyzable β-blocker. When the meta-analysis was repeated excluding the study of Weir et al[8] from quantitative data synthesis, the use of a highly dialyzable β-blocker was associated with 13% reduced risk of all-cause mortality (HR, 0.87; 95% CI, 0.80-0.94) and with 13% reduced risk of adverse cardiovascular events (HR, 0.87; 95% CI, 0.84-0.91).[5] Contrary to the original hypothesis that high dialyzability would limit the therapeutic efficacy of β-blockers and would aggravate the risk of adverse events, the use of highly dialyzable β-blockers was shown to be associated with reduced cardiovascular morbidity and all-cause mortality.

The question that arises is whether dialyzability is the sole factor that can fully explain this potential benefit. It has to be noted that exposure to β-blockers was not randomly allocated in the studies that were included in the meta-analysis of Tella et al.[5] The observational nature of these meta-analytic data precludes the opportunity to derive a direct cause-and-effect association between

β-blocker dialyzability and risk of adverse cardiovascular events and mortality. On a closer examination, the high-dialyzability groups in these studies enrolled patients who were being treated mainly with cardioselective β-blockers, such as atenolol and metoprolol.[6,7,9] In contrast, the low-dialyzability groups included patients receiving predominantly therapy with noncardioselective β-blockers, such as carvedilol, labetalol, or propranolol.[6,7,9] Accordingly, differences in other pharmacologic characteristics of β-blockers that were compared, such as the difference in β_1 cardioselectivity, may also be responsible for the observed cardioprotective benefit of highly dialyzable β-blockers.

If we assume that a causal association between the use of highly dialyzable β-blockers and reduced risk of adverse cardiovascular outcomes truly exists, it may be preferable to prescribe highly dialyzable β-blockers in daily clinical practice. The design of an appropriate dosing regimen relative to the timing of intermittent hemodialysis is then required to reassure that dialytic clearance will not result in subtherapeutic plasma concentrations of the drug during the interdialytic period. A practical approach is to administer β-blockers with high dialyzability after the completion of hemodialysis and to tolerate low plasma concentrations of the drug during the hemodialysis procedure to mitigate the risk of adverse intradialytic events, such as symptomatic hypotension.[4] This dosing regimen is particularly applicable to highly dialyzable β-blockers with a sustained and prolonged duration of action, such as atenolol, for which pharmacokinetic studies showed a dialytic clearance value as high as 167 mL/min and an elimination half-life of 100 hours in patients with kidney failure.[11,12]

Taking into consideration these unique pharmacokinetic properties, Agarwal et al[13] conducted a single-arm interventional study aiming to investigate the safety and blood pressure (BP)–lowering efficacy of supervised atenolol therapy in 8 patients receiving hemodialysis with uncontrolled hypertension, as confirmed by the "gold-standard" method of 44-hour interdialytic ambulatory BP monitoring. Atenolol was administered at an initial dose of 25 mg (titrated up to 100 mg) by a nurse 3 times a week immediately after the completion of hemodialysis. Over a follow-up period of 3 weeks, the 44-hour ambulatory systolic BP was significantly reduced from 144 ± 14 to 127 ± 13 mm Hg ($P < 0.001$) and the 44-hour heart rate fell from 85 ± 11 to 70 ± 11 beats/min ($P < 0.001$).[13] The BP-lowering efficacy of atenolol persisted over the entire 44-hour interdialytic interval. This potent reduction in interdialytic ambulatory BP was not accompanied by a higher incidence of intradialytic symptomatic or asymptomatic hypotensive episodes,[13] possibly because of the high removal of atenolol by the filter during hemodialysis.

Stronger evidence to support the BP-lowering efficacy and cardiovascular safety of the highly dialyzable β-blocker atenolol was provided by the hypertension in hemodialysis treated with atenolol or lisinopril (HDPAL) trial.[14] In this trial, 200 patients receiving hemodialysis with echocardiographically documented left ventricular hypertrophy and hypertension were randomized to open-label therapy with atenolol (25-100 mg) or lisinopril (10-40 mg). Because both atenolol and lisinopril have high dialytic clearance, they were administered thrice weekly immediately postdialysis. Over 12 months of follow-up, the 44-hour ambulatory BP improved similarly in the atenolol and lisinopril groups. However, atenolol appeared to exert a more potent BP-lowering effect, as monthly monitored home BP was consistently higher over time in patients treated with lisinopril, despite the requirement for both a greater intensification of background antihypertensive therapy and a greater reduction in dry weight. Most importantly, the HDPAL trial[14] was prematurely terminated because of cardiovascular safety reasons. The combined safety outcome of nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization occurred more commonly in the lisinopril group than in the atenolol group (incidence rate ratio, 2.29; 95% CI, 1.07-5.21).[14] Although the abrupt intradialytic removal of highly dialyzable β-blockers is considered a predisposing factor for serious arrhythmias and cardiac arrest, these adverse events occurred rarely with the postdialysis administration of atenolol over the 1-year-long course of the HDPAL trial.[14]

In conclusion, should we use highly dialyzable β-blockers in patients on hemodialysis? The meta-analysis of 4 retrospective observational studies that was conducted by Tella et al[5] provides evidence that, compared with poorly dialyzable β-blockers, the use of highly dialyzable β-blockers may be associated with a lower risk of adverse cardiovascular events and all-cause mortality. Critically, there was no evidence of harm with the use of highly dialyzable β-blockers. In addition, the HDPAL trial[14] also supports the BP-lowering efficacy and cardiovascular safety of the highly dialyzable β-blocker atenolol when this agent is administered sensibly as a thrice-weekly regimen immediately postdialysis. These preliminary data call for a properly designed, randomized controlled trial that will definitively elucidate the comparative effectiveness between highly dialyzable and poorly dialyzable β-blockers in this high-risk patient population.

ARTICLE INFORMATION

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