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Strength of evidence for labeled dosing recommendations in renal impairment

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Abstract

Background/Aims: Renally excreted medications often require dose adjustment in patients with kidney impairment. While drug development and approval in the United States are typically based on several Phase I and II studies and one or more larger Phase III randomized trials, the basis for labeled dosing recommendations for patients with renal impairment is less well known. In response, we aimed to quantify the level of evidence used to recommend labeled dosing adjustments for newly approved drugs in patients with renal impairment.

Methods: We reviewed publicly available drug labels and approval packages for new molecular entities approved in the United States between 2012 and 2014. The sample was restricted to 29 renally excreted new molecular entities that were not granted orphan drug status. We extracted data regarding approved indications, normal dosing, dosing adjustments for patients with mild (estimated glomerular filtration rate >60 mL/min/1.73 m^2), moderate (estimated glomerular filtration rate 30–<60 mL/min/1.73 m^2), and severe (estimated glomerular filtration rate <30 mL/min/1.73 m^2) renal impairment, characteristics of studies used to justify dosing adjustments, and numbers of subjects in each study.

Results: In all, 14 of 29 (48%) new molecular entities had labels that recommended dosing adjustments for patients with mild, moderate, and/or severe renal impairment. Among these 14 new molecular entities, 4 (29%) used only pharmacokinetic studies to justify the recommendations, with no examination of clinical outcomes for patients with renal impairment. Where data were available, the median number of patients with renal impairment evaluated in studies used for dosing adjustment was 34 (range, 4–5976). Of the 15 new molecular entities with no recommended dosing adjustments for this population, 2 (13%) did not report assessing the effects of renal impairment.

Conclusion: Nearly half of newly approved renally excreted drugs include dosing adjustments for kidney impairment on the label, but the recommendations are usually based on very small numbers of patients and often utilize pharmacokinetic studies alone. More research is needed to understand the benefits and risks of new drugs in patients with renal impairment.

Keywords

Renal impairment, dosing adjustment, drug label

Introduction

Medications that are renally excreted often require dose adjustment for patients with renal impairment, which affects 1 in 10 adults in the United States.[1] It is well known that many randomized trials that evaluate the efficacy and safety of medications exclude patients with kidney disease, even though these patients are disproportionately affected by chronic conditions that the drugs are intended to treat.[2] For new drug approval, the US Food and Drug Administration (FDA)[3] recommends pharmacokinetic studies in patients with renal impairment for drugs with $\geq$30% renal excretion, but does not require trials examining clinical outcomes to support dosing recommendations for patients with renal impairment that ultimately appear on drug labels. For example, the recommended dose of dabigatran for reduction in risk of stroke and systemic embolism in non-valvular atrial fibrillation for patients with severe renal impairment is 75 mg twice daily. However, this

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Table 1. Numbers of patients with renal impairment evaluated for renally excreted drugs with labeled dosing adjustments.

Year	No. of drugs with dosing adjustments	No. of drugs with dosing adjustments for mild renal impairment	Median number (range) of patients in studies	No. of drugs with dosing adjustments for moderate renal impairment	Median number (range) of patients in studies	No. of drugs with dosing adjustments for severe renal impairment	Median number (range) of patients in studies
2012	4/8 (50%)	1/8 (13%)	20 (N/A)	3/8 (38%)	6 (4–8)	4/8 (50%)	7 (0–12)
2013	4/11 (36%)	1/11 (9%)	0 (N/A)[a]	4/11 (36%)	11 (0–1317)	4/11 (36%)	8 (4–16)
2014	6/10 (60%)	0/10 (0%)	N/A	4/10 (40%)	539 (5–1607)	6/10 (60%)	9 (0–175)
Total	14/29 (48%)	2/29 (7%)	10 (0–20)	11/29 (38%)	7 (0–1607)	14/29 (48%)	7 (0–175)

N/A: not applicable.

[a]One drug was "not recommended" for patients with mild renal impairment even though no patients with mild renal impairment were studied.

dose was not evaluated in the pivotal Phase III trial, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),[4] that was the basis of market authorization of dabigatran. In FDA's[5] pharmacology review that was performed as part of the approval process, it was noted that, "… there is no efficacy or safety information available at the proposed dosing regimen of 75 mg dabigatran QD in severe renal impairment."

While prescribers and patients rely on such labeled dosing information for making important treatment decisions in patients with renal impairment, the evidence base for the recommendations is not well known. Therefore, we conducted a systematic review to quantify this evidence base supporting labeled dosing recommendations for patients with renal impairment for newly approved drugs.

Methods

We obtained data from the Drugs@FDA database[6] and identified all new drugs, defined as new molecular entities approved between 2012 and 2014 (Table 1). We excluded orphan drugs and those with $<30\%$ renal excretion or not primarily metabolized in bile. For each eligible drug, we accessed the drug approval packages and most recent drug label and determined whether dosing adjustments were recommended for patients with renal impairment. We then used the labels and approval packages—which often contain multiple documents, including approval letters, medical reviews, chemistry reviews, pharmacology reviews, and statistical reviews—to identify the studies, if any existed, that formed the basis of dosing adjustment recommendations for patients with mild (estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2), moderate (eGFR 30 to <60 mL/min/1.73 m^2), and severe (eGFR <30 mL/min/1.73 m^2) renal impairment.

Results

In all, 29 eligible, renally excreted drugs were approved between 2012 and 2014. For 27 of the drugs, the labels indicated the fraction of the drug that is renally excreted. Of these, 13 were more than 50% renally excreted, including 5 that were more than 80% renally excreted. In all, 14 of 29 (48%) had labels that recommended dosing adjustments for patients with renal impairment, including five drugs that were not recommended and two that were contraindicated in these patients. Across these 14 drugs, the median number of patients with renal impairment evaluated was 34 (range, 4–5976); median values were 10 (range, 0–20) for mild renal impairment, 7 (range, 0–1607) for moderate renal impairment, and 7 (range, 0–175) for severe renal impairment. Four (29%) used only pharmacokinetic studies to justify the recommendations, with no examination of clinical outcomes for patients with renal impairment as patients with renal impairment were excluded from Phase II and III trials. Of the 15 drugs with no recommended dosing adjustments for renally impaired patients, 2 (13%) did not report assessing the effects of renal impairment, despite FDA's guidance.

Discussion

Our study highlights the limited evidence base on which labeled dosing recommendations are made for patients with renal impairment. We found that, while nearly half of newly approved drugs included dosing adjustments for renal impairment in their labels, on average, these recommendations were based on very small numbers of patients and often relied on pharmacokinetic studies alone, without including patients with renal impairment in Phase II and III studies that evaluated clinical outcomes. For 13% of drugs with no recommended dosing adjustments, we were unable to find evidence that the impact of renal function on drug exposure was assessed at all, even in pharmacokinetic studies.

Prior reviews have documented the proportion of new drug applications that contain renal impairment study data and recommended dosing adjustments in renal impairment.[7–9] However, ours is the first to quantify the numbers of patients with renal impairment

included in studies on which labeled doing recommendations are based. While our review relied on publically available information from drug labels and drug approval packages, and it is possible that studies of these drugs in renally impaired patients have been conducted but not reported in these documents, these resources—and the label, in particular—reflect the body of information typically available to physicians and pharmacists at the time of drug prescribing and dispensing.

While FDA recommends pharmacokinetic studies in patients with impaired renal function for drugs that are substantially renally eliminated, it does not require or even recommend studies of clinical outcomes to justify recommendations for dosing adjustments in patients with renal impairment. Requiring definitive efficacy and safety information at every level of renal impairment prior to drug approval is impractical. However, while it is reasonable to expect that similar drug concentrations achieved by different doses will likely result in similar clinical outcomes, large observational studies can provide reassurance that, with dose adjustments, patients with renal impairment attain the same clinical benefits of medications without an increase in risk of adverse events.[10] Such pharmacoepidemiologic studies conducted in secondary electronic healthcare databases can be conducted quickly and at relatively low cost.[11] Moreover, while drug labels state recommendations about dosing adjustments, they do not typically describe the evidence on which the recommendations are based. This information should be presented in the label so that prescribers, pharmacists, and patients can be made aware of the strength of evidence available to support critical treatment decisions for patients with impaired renal function.

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References

1. Centers for Disease Control and Prevention. National chronic kidney disease fact sheet, 2014, http://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf (accessed 23 February 2016).
2. Konstantinidis I, Nadkarni GN, Yacoub R, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med* 2016; 176: 121–124.
3. US Food and Drug Administration. Guidance for Industry: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling, http://www.fda.gov/downloads/Drugs/./Guidances/UCM204959.pdf (2010, accessed 21 February 2016).
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.
5. US Food and Drug Administration. *Clinical pharmacology and biopharmaceutics review(s)*. Application No. 22–512. Center for Drug Evaluation and Research, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000ClinPharmR_Corrrected%203.11.2011.pdf (2010, accessed 29 April 2016).
6. Drugs@FDA. US Food and Drug Administration, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (accessed 21 January 2016).
7. Zhang Y, Zhang L, Abraham S, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. *Clin Pharmacol Ther* 2009; 85: 305–311.
8. Dowling TC, Matzke GR, Murphy JE, et al. Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. *Pharmacotherapy* 2010; 30: 776–786.
9. Matzke GR, Dowling TC, Marks SA, et al. Influence of kidney disease on drug disposition: an assessment of industry studies submitted to the FDA for new chemical entities 1999-2010. *J Clin Pharmacol* 2016; 56: 390–398.
10. Vardi M, Yeh RW, Herzog CA, et al. Strategies for postmarketing surveillance of drugs and devices in patients with ESRD undergoing dialysis. *Clin J Am Soc Nephrol* 2013; 8: 2213–2220.
11. Gagne JJ, Glynn RJ, Rassen JA, et al. Active safety monitoring of newly marketed medications in a distributed data network: application of a semi-automated monitoring system. *Clin Pharmacol Ther* 2012; 92: 80–86.