

Challenges of prescribing low-dose drug therapy for older people



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Elderly patients are at greater risk for adverse drug effects than younger people. Advanced age, use of multiple medications,^{1,2} coexisting conditions,² low body weight and being a woman³ have all been proposed as factors in this difference. Because most adverse effects are related to dose, conventional wisdom holds that drug therapy should be initiated at low doses. However, clinicians face several challenges when prescribing low-dose therapy for their older patients.

In this article we present 3 clinical scenarios to illustrate some of these challenges. The first scenario describes the use of thiazide diuretic therapy for the treatment of hypertension and illustrates the difficulty of prescribing low-dose therapy when only a limited range of tablet sizes is available. The second scenario, use of β -blocker therapy for secondary prevention after myocardial infarction, illustrates the difficulty of choosing the appropriate dose when randomized controlled trials (RCTs) have not evaluated the minimum effective dose. The final scenario, use of warfarin therapy for lone atrial fibrillation, illustrates the importance of not confusing low-dose therapy with inappropriate suboptimal dosage.

Thiazide diuretics: Start low, stay low

The case

An 85-year-old woman with hypertension comes to your office. You wish to initiate drug therapy for her high blood pressure, and you consult the Canadian consensus guidelines for the treatment of uncomplicated hypertension.⁴ On the basis of these recommendations you write a prescription for 12.5 mg of hydrochlorothiazide (HCTZ) daily. The next day you get a call from the patient, who tells you that she was given 25-mg tablets of HCTZ and was told to take half a pill daily. She is having difficulty breaking the pills.

Comments

The use of thiazide diuretics to manage hypertension is an example of a drug therapy that should be started and continued at a low dose. RCTs have shown that these agents are effective at low dosages.⁵⁻⁹ Accordingly, evidence-based guidelines for the treatment of uncomplicated hypertension in both Canada⁴ and the United States¹⁰ recommend that HCTZ be initiated at a low dose (12.5 mg by mouth once daily).

The need to use the lowest effective dose of a thiazide diuretic is underscored by the dose-related adverse effect profile. Thiazides are among the top 10 drugs causing adverse drug reactions.^{11,12} Wikstrand and associates¹³ reported that 21% of patients receiving higher dosages (i.e., 50 mg daily of HCTZ) experienced hypokalemia. Furthermore, higher thiazide dose has been associated with an increased need for anti-gout therapy.¹³

Case resolution

Prescribing HCTZ at a low dose is an appropriate starting point for the treatment of hypertension in this patient. Unfortunately, the current limited availability of tablet sizes means that your patient, her caregiver or her pharmacist must break

Education

Éducation

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the pills to obtain the prescribed dose. This puts the patient at unnecessary risk for an adverse drug effect caused by inaccurate dosing and may increase the likelihood of non-compliance with the therapy.

β -Blocker therapy: Start low, but where to go?

An 80-year-old man is in hospital after acute myocardial infarction. He is fit and has no history of congestive heart failure, chronic obstructive pulmonary disease or diabetes mellitus. You would like to initiate β -blocker therapy because you understand that this therapy may reduce the risk of death by 25%.¹⁴ You review the major RCT documenting the benefit of metoprolol for secondary prevention after myocardial infarction¹⁵ and learn that the dose evaluated in that trial was 100 mg twice daily. Your colleagues who frequently care for older patients tell you that they use much lower doses. You want to initiate the drug but don't know what dose to use.

Comments

For many drug treatments the optimal dosage for seniors has not been evaluated in clinical trials, nor has the minimum effective dose been established. β -Blockers are widely recommended by experts as therapy for all patients who have experienced myocardial infarction and who have no contraindications to this treatment. Despite these recommendations, β -blockers have been underused in elderly people,¹⁶⁻¹⁸ which has been associated with significantly increased rates of death and re-admission to hospital relative to β -blocker recipients.¹⁸

Possible reasons for underuse of β -blocker therapy include fear of unwanted drug effects in older patients. There is a lack of information on the minimum dose of β -blockers that is effective in preventing re-admission to hospital and death yet minimizes the risk of adverse effects.^{19,20} The major RCTs of β -blocker therapy in survivors of myocardial infarction^{15,21-23} used relatively high doses. Furthermore, like RCTs evaluating a range of other drug therapies,²⁴⁻²⁷ trials of therapy for cardiovascular conditions²⁴ have systematically excluded seniors. Concern about potential adverse drug effects may result in many seniors not receiving a trial of β -blocker therapy, or, if such therapy is initiated at dosages that are too high, intolerance of the drug may necessitate rapid discontinuation.

Case resolution

Given the proven benefit of β -blocker therapy, it is important to initiate this therapy in your patient. The prudent approach would be to start β -blocker therapy at a low dose (e.g., metoprolol 12.5 mg by mouth twice a day), carefully monitoring for side effects and then increasing the dosage as tolerated. Future clinical trials of β -blocker therapy should evaluate the lowest effective dose to improve survival among older patients who have had myocardial infarction.

Warfarin therapy: Start low, but reach the goal

The case

A 75-year-old woman with lone atrial fibrillation is being examined in your office, and her current medications are being evaluated. She is taking warfarin at low dosage (1.0 mg daily). Her international normalized ratio (INR) has been maintained at about 1.5 since treatment was initiated 6 months ago.

Comments

Evidence suggests that, when warfarin is given to older patients with atrial fibrillation, therapeutic INR levels must be reached and maintained (target INR 2-3) to prevent stroke.²⁸⁻³¹ Subtherapeutic INR is not as effective in protecting against ischemic stroke in the setting of atrial fibrillation.²⁹⁻³¹ In practice, older patients may require lower dosages of warfarin than younger patients to maintain a therapeutic INR level.¹

In previous work, in which we evaluated patterns of prescription of warfarin to frail older people with atrial fibrillation living in long-term care institutions in Canada and the United States, we found that in almost half of the patients (44.8%), INR levels were maintained below the established therapeutic range.³² When asked, many physicians caring for older people in both primary care³³ and long-term care³⁴ settings reported that they felt more comfortable with a target therapeutic range below the level currently recommended. This example illustrates that initiating an "effective" therapy is only the first part of the prescriber's responsibility; dosages must be titrated to ensure that therapeutic goals are achieved.

Case resolution

Older patients, such as this one, often require low doses of warfarin to reach desired INR levels. However, it is important to titrate the dose so that the target INR level is reached. The dose of warfarin should be selected to maintain the patient's INR between 2 and 3. The wide range of warfarin tablet sizes available facilitates selection of the correct dose.

Conclusion

Conventional wisdom supports the use of lower doses when prescribing drug treatment for older patients. The degree to which the dose is reduced depends on the medication and the clinical situation. For some medications, such as thiazide diuretics for the treatment of uncomplicated hypertension, low doses have been evaluated in clinical trials and found to be effective. For other medications, such as β -blockers for secondary prevention of myocardial infarction, a low dose is probably the appropriate starting point, but the optimal dose is unknown. Finally, for drugs



such as warfarin, for which trial-based therapeutic ranges have been established, the use of low doses should not be confused with the need to reach the target therapeutic range.

Lower-dose formulations of medications commonly used by older patients are needed to meet the special needs of this group. The costs for such lower-dose formulations should be comparable to those of currently available higher-dose formulations, so as not to increase the financial burden on older persons.

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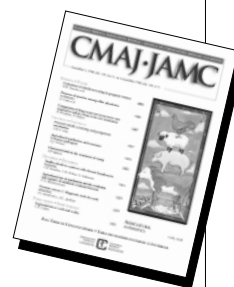
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