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European Association of Urology

Understanding Dose Titration: Overactive Bladder Treatment With Fesoterodine as an Example

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Article info

Keywords:
Dose response
Fesoterodine
Muscarinic antagonists
Overactive bladder
Pharmacodynamic
Pharmacokinetic

Abstract

Context: Individuals differ in their sensitivity to drug treatment, including that with muscarinic receptor antagonists used in the treatment of overactive bladder (OAB), due to a combination of pharmacodynamic and pharmacokinetic reasons.
Objective: To discuss the variability in drug response among individual patients, the concept of the dose-response curve, and the selection of drug dosage as well as how these factors are integrated when optimising OAB treatment using the muscarinic receptor antagonist fesoterodine as an example.
Evidence acquisition: Data sources were identified in 2010 using a nonsystematic search and included articles and abstracts selected using expert opinion of their relevance to drug response in OAB.
Evidence synthesis: A given drug dose is unlikely to yield the same quantitative response in all patients, and undertreatment (too little efficacy) or overtreatment (too many side effects) may occur. The position and shape of the dose-response curve for a drug may differ between patients and within a patient for desired and adverse effects. The availability of two or more drug doses allows for titration (flexible dosing) to find the dose exhibiting the optimal clinical efficacy that is tolerable for an individual patient. Optimally, a patient would have symptom resolution with no adverse events (AEs). Realistically, an efficacy-to-tolerability ratio (therapeutic index) exists for each of the combinations of selected efficacy metrics and AE reports.
Conclusions: Dose titration is important for selection of an effective dose of a treatment with minimal side effects.

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1. Introduction

Overactive bladder syndrome (OAB) is a prevalent condition with an adverse impact on the quality of life of the affected patients and their partners [1]. Muscarinic receptor antagonists are the mainstay of pharmacologic OAB treatment [2]. Although effective for many patients, the use of antimuscarinics can be associated with adverse events (AEs) such as dry mouth or constipation [2]. Of note, on initial observation, patients may appear to have either a limited response to standard doses of antimuscarinics (low efficacy and low AEs) or may be sensitive to antimuscarinic agents (high efficacy, possibly accompanied by high AEs). On more careful inspection, there are multiple permutations of response because the individual dose-response curves for the selected efficacy metrics and the observed

1569-9056/$ – see front matter doi:10.1016/j.eursup.2011.01.004

AEs are not similar and are not linear, producing varying individual clinical responses. The clinical extremes are the patient who attains full resolution of OAB symptoms with no AEs and the patient who experiences intolerable AEs with no clinical response. The clinical ideal is a dosage range that allows a trade-off between efficacy and tolerability and provides the option in most patients to titrate to the desired level of either or both. Therefore, it is necessary to find the optimal treatment for each individual patient, and drugs that provide individual dose titration are advantageous in such situations. Against this background, we will summarise multiple potential factors that may be involved in interindividual differences in antimuscarinic sensitivity, relate these to the concept of the dose-response curve, and illustrate these scenarios with the muscarinic receptor antagonist fesoterodine, an agent used in OAB treatment.

2. Evidence acquisition

Data sources were identified in 2010 using a nonsystematic search of Medline (using the generic names of muscarinic antagonists used in OAB treatment as search terms), 2008–2010 abstract volumes of major urology journals, and standard pharmacology textbooks. From this search, articles and abstracts were selected by their relevance to drug response in OAB.

3. Evidence synthesis

3.1. Interindividual differences in sensitivity to antimuscarinics

The quantitative response to a drug, such as a muscarinic antagonist, can vary between patients due to a combination of pharmacodynamic (PD) and pharmacokinetic (PK) factors. *Pharmacodynamics* describes what a drug does to the organism, whereas *pharmacokinetics* describes what the organism does with the drug, mostly the processes of absorption, distribution, metabolism, and elimination (ADME).

Reasons for PD variability between patients include alterations of receptor expression due to age or concomitant disease [3] or based on genotype [4]. Concomitant medications that act on muscarinic receptors may also contribute to PD variability [5]. PD causes of differential response typically apply to all members of a drug class acting on a given molecular target (eg, a muscarinic receptor).

PK causes of response variability between patients, either in the entire body or in individual compartments, relate to exposure to different drug concentrations on ingestion of the same dose. They can have their effects at all stages of pharmacokinetics (ie, ADME). At the absorption level, this can involve interactions with food, for example, as demonstrated for some α_1-adrenoceptor antagonists [6]. At the distribution level, binding to plasma proteins [7] or penetration through the blood–brain barrier (BBB) [8] can contribute to variability of drug response in the entire body or specific compartments. Variability at the level of drug metabolism can occur from hepatic impairment or may be based on genetic polymorphisms of drug-metabolising enzymes, particularly CYP 2D6 [9], or by induction or inhibition of these enzymes by concomitant medication [10]. At the excretion level, differences in renal function may contribute to drug exposure, particularly for drugs that are excreted largely by the kidneys [11]. In contrast to PD causes of differential drug response, PK causes are not necessarily shared by all members of a drug class but rather relate to the specific chemical properties of a given drug and, for this reason, can differ between compounds within a drug class [12].

In clinical practice, many if not most of the PD and PK factors contributing to interindividual differences in sensitivity to antimuscarinics are unknown for an individual patient. This means that treatments must be tried for the patient to find a specific drug and dose that serves the patient with a personally optimised efficacy-to-tolerability ratio.

3.2. The concept of the dose-response curve

Finding the right dose for a given patient is not only a question of efficacy but rather of the efficacy-to-tolerability ratio. This is important because AEs are a major reason for patient dissatisfaction and discontinuation of treatment [13]. Both desired effects and AEs exhibit specific dose-response curves that are not necessarily the same (Fig. 1). It is possible, for example, that a drug target may be differentially regulated in tissues mediating desired effects and AEs [14]. Additionally, the underlying PK reasons for differential drug exposure may not have the same result in each body compartment, for example, due to distribution barriers such as the BBB. A differential dose-response curve for desired effects and AEs is the basis for functional "uroselectivity" [15].

To understand this, it is necessary to take a closer look at the principles behind a dose-response curve. There are two types of dose-response curve. In most cases, dose-response curves are graded (ie, with increasing dose, the effect increases). This can relate to a dose-dependent improvement of OAB symptoms but also to the intensity of an AE such as the intensity of dry mouth with muscarinic antagonists. Additionally, examples exist where an increasing dose is not associated with a greater response but with a more likely response (eg, a greater likelihood of any dry mouth with a greater drug dose). For simplicity, we will primarily focus on graded drug responses in this manuscript, but the same principles are also applicable to nongraded responses with some minor modifications.

A given drug dose yields a given exposure to this drug for a given patient at a specific point in time. Changes in exposure at the very low end or the very high end of the dose-response curve have only a small effect on the response (Fig. 1). In contrast, if exposure is close to the middle part of the dose-response curve, changes in drug dose can have major effects on response. This can be seen as the "sweet spot" of the dose-response curve, where a response can be titrated to the desired level (assuming sufficient dosing options are available). Unfortunately, we