Maturitas xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Medicines optimisation in older people: Taking age and sex into account

Catherine Lucas[a], Julie Byles[b], Jennifer H. Martin[c,*]

[a] Clinical Pharmacologist, School of Medicine and Public Health, University of Newcastle, New South Wales, Australia
[b] Head of Public Health, School of Medicine and Public Health, University of Newcastle, New South Wales, Australia
[c] Chair of Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, New South Wales, Australia

ARTICLE INFO

Article history:
Received 10 June 2016
Accepted 25 June 2016
Available online xxx

Keywords:
Polypharmacy
Drug prescriptions
Drug interactions
Inappropriate prescribing
Aged
65 and over
Female

ABSTRACT

There are a number of complex and seemingly ignored issues around prescribing safely and effectively for older people, particularly for very old women. These issues include polypharmacy, possible compliance issues and communication barriers between patient, specialists and general practitioners (GPs). There are specific pharmacokinetic (PK) and pharmacodynamic (PD) parameters that change in older age generally, and in women more specifically, which if ignored are likely to cause symptoms and to impair quality of life when drug dosage is unchanged. These changed PK and PD parameters are not all-or-nothing processes, but a continuum across age, sex and comorbidity.

Very old people also have less 'reserve' when drugs are used in 'standard' doses, are more likely to have multiple concurrent therapies, and the risk of adverse effects of drugs in this group is very high. Doctors need to consider these issues when providing therapy for this group, or when trying to unravel the complex prescribing cascade here. This review outlines general principles to consider when prescribing for older people, focusing on age- and sex-related changes in both PK and PD processes.

Contents

1. Introduction 00
2. Methods 00
3. Pharmacokinetics 00
   3.1. Absorption of oral medications 00
   3.2. Distribution 00
   3.3. Metabolism 00
      3.3.1. Importance of synthetic function 00
      3.3.2. Importance of hepatic metabolic process 00
   3.4. Excretion 00
4. Pharmacodynamics 00
   4.1. PD changes that cause adverse drug effects 00
      4.1.1. Adverse drug reactions (ADRs) 00
      4.1.2. Drug interactions 00
   4.2. Poly and hyper-polypharmacy 00
   4.3. Compliance 00
   4.4. Detection of adverse events 00
   4.5. Appropriate medication decision support 00
5. Conclusion 00
Contributors 00
Conflict of interest 00

* Corresponding author.
E-mail address: jen.martin@newcastle.edu.au (J.H. Martin).

http://dx.doi.org/10.1016/j.maturitas.2016.06.021
0378-5122/

Funding 00
Ethical approval 00
Provenance and peer review 00
Acknowledgement 00
References 00

1. Introduction

Most drugs used in clinical practice have never had their pharmacokinetic (PK) and pharmacodynamic (PD) properties studied in older people, specifically not in the over 75 years age group or in those with additional comorbidity or frailty. It is not a requirement of regulatory authorities to do so, and most studies enroll patients under 70 and without common comorbidities which cause altered PK and PD. The ICH/European Guideline Clinical Investigation of Medicinal Products in Geriatrics [1] gives some Guidance to Industry around the registration of new active substances that are likely to have significant use in older people, either because the disease intended to be treated is characteristically a disease of ageing or the population to be treated is known to include substantial numbers of geriatric patients, or if there are reasons to expect that conditions common in older people (e.g. organ impairment, concomitant illnesses or medications) may alter the geriatric patient's response (with regard to either safety/tolerability or efficacy) compared with that of the non-geriatric patient. This Guideline states that geriatric patients should be included in the Phase III database (and in Phase II, 'at the Sponsor's option') in meaningful numbers. However many 'new' therapies, for example cancer therapies, may come to registration on Phase II data only. In practice, the geriatric data may be 'simulated' from other populations or translated from healthy geriatric volunteers rather than actual data from a geriatric population with common comorbidity. Further, the PK data, if available, is usually based on single or short-term dosing as distinct from the long-term use and with concomitant therapies usual in older people. It is noted that this Guideline does not require information on existing agents in clinical use.

In addition to the often limited trial data of these drugs in older people, it can be difficult for investigator initiated studies, such as those collecting post marketing pharmacovigilance studies in older people, to receive non-industry funding to provide the much needed evidence. This may be because of the complexity of both the pharmacology issues and the heterogeneous population, which can span a 40-year age period, requiring large numbers of otherwise homogeneous older people to reduce confounding. It is also difficult to conduct large Industry-sponsored randomised controlled trials in older patients as side effects and withdrawals are likely to be much larger than a younger healthier population, potentially threatening registration. Further, many older patients have multiple morbidities and take many different medications that cannot be discontinued so that a patient can participate in a drug study. Therefore, paradoxically, while drugs are more likely to be used in older patients who have higher prevalence of disease, listing is more likely (and the clinical trial size much smaller) for a Sponsor if the clinical studies focus on a homogeneous, healthier and younger population likely to better tolerate the drug. The aim of this Review is thus to focus on general principles for prescribers to consider when prescribing for older people, focusing on age and sex-related changes in both PK and PD processes.

2. Methods

Methodology was adherent to the PRISMA-P 2015 reporting guideline for systematic review protocols [2] (Fig. 1). A literature search performed via the health science database Embase® (1974–2016) via Ovid, using the strategy *drug monitoring/or *drug/or *recommended drug dose/or *drug exposure/or *drug dose regimen/or *drug incompatibility/or *drug therapy/or *adverse drug reaction/or *oral drug administration/or *drug dose increase/or drug metabolism/or *drug potency/or *drug accumulation/or *drug activity/or *drug dose/or *drug clearance ratio/or *drug combination/or *drug toxicity/or *"drug toxicity and intoxication"/or *drug interaction/or *drug dose titration/or drug induced disease/or *drug uptake/or *maintenance drug dose/or *drug fatality/or *drug elimination/or *drug absorption/or *drug efficacy/or *acute drug administration/or *drug effect/or *drug dose comparison/or drug blood level/or *prescription drug/or drug dose escalation/or *drug clearance/or *drug contraindication/or *drug dose reduction/or *drug tolerability/or *low drug dose/or *drug concentration/or *drug choice/and limited to aged <65+ years>, English-language and humans, elicited 35305 results. EndNote™ reference management software was employed to de-duplicate references and subsequently, 1499 titles were selected and all abstracts reviewed for relevance to this Review. A title keyword search of the reviewed abstracts (using the terms gender; sex; female and women) yielded 20 articles relevant to the specific focus of the Review. Further; additional relevant references cited within these articles were sourced.

An additional search performed via the Cochrane Library, using the strategy (drug OR medicine OR prescri*) AND (old* OR elder* OR geriatric) yielded 473 reviews, 3 of which were relevant.

3. Pharmacokinetics

Pharmacokinetics (PK) describes how a person processes a specific drug after its administration. Route of administration is very important as although there is often knowledge about the population relationship between plasma concentrations after e.g. intravenous or oral dosing, the ratio may differ in a particular older patient depending on other comorbidity including gut function, type of diet, concurrent medication that affects gut transit time (such as prokinetic agents) and chemical issues such as concurrent proton pump inhibitor administration. Timing and frequency can also affect target drug concentrations (Table 1).

In addition, every therapeutic has a PK profile based on specific parameters such as age, sex, weight, body mass index, hepatic function, and renal function, inter alia. The effect of sex may be predominantly related to body composition, however, sex can be the important covariate to understand if body composition parameters are not available. PK differences attributable to sex include generally lower body weight and organ size, higher body fat percentage (regardless of age) and lower normalised glomerular filtration rate (GFR) in women relative to men [3].

Overall the PK of most medications in older adults has not been studied in enough detail to recommend use or at least correct dose in older or very old patients. Therefore, having enough knowledge of the principles of PK (absorption, distribution, metabolism, and elimination) in general and in a particular patient can help make reasonable predictions about likely PK to support a decision about dosing and timing.

Please cite this article in press as: C. Lucas, et al., Medicines optimisation in older people: Taking age and sex into account, Maturitas (2016), http://dx.doi.org/10.1016/j.maturitas.2016.06.021