Drug interactions and their potential toxic effects among patients in Gjilan region, Kosovo

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Abstract

In the public health and medical field, but more specifically in the clinical settings, particular attention should be made in order to avoid adverse drug interactions and their potential toxic effects. In any case, regardless of the efforts to avoid drug interactions and their resulting toxic effects, for individuals taking at least two medications (drugs), the risk of a drug interaction has been estimated at 15%. On the other hand, for individuals taking at least five medications the risk of adverse drug interactions increases up to 40%. Finally, for individuals taking at least seven medications the risk amounts to a disturbing 80%.

Hence, the risk of a toxic medication interaction is real considering that more than one half of non-institutionalized adults older than 65 years take five or more different medications, and 12% use ten or more medications. In the United States of America, among the hospitalized patients, adverse drug interactions are estimated to be as high as the fourth leading cause of death.

Toxic drug interactions can occur when two or more medications compete in such a way that their pharmacologic interaction causes a detrimental physiologic response. Alternatively, toxic drug interaction can occur when a medication is prescribed in excessive amounts, or when one medication produces inconvenient consequences although it is prescribed according to established guidelines. It has been argued that this last effect is often the most difficult to predict because drug absorption and metabolism can vary with age, concomitant illness, gastric motility, pH of the gastrointestinal milieu, genetic variation, smoking, or some other obscure physiologic parameter.

It has been demonstrated that the most dangerous drug combinations in the nursing home population involve warfarin interactions with non-steroidal anti-inflammatory drugs (NSAIDs), sulfonamides, macrolides, or quinolones; angiotensin-converting enzyme (ACE) inhibitor interactions with potassium supplements or spironolactone; digoxin interactions with amiodarone; and theophylline interactions with quinolones.

However, the available information on drug interactions and their health effects is scarce for Kosovo including Gjilan region. In this framework, there is an obvious need to conduct population-based studies assessing the potential toxic effects of drug interactions in Kosovo, a post-war country in the Western Balkans.

Keywords: drug interactions, Gjilan region, Kosovo, toxic effects.

Introduction

In the public health and medical field, but more specifically in the clinical settings, particular attention should be made in order to avoid adverse drug interactions and their potential toxic effects. In any case, regardless of the efforts to avoid drug interactions and their resulting toxic effects, for individuals taking at least two medications (drugs), the risk of a drug interaction has been estimated at 15% (1,2). On the other hand, for individuals taking at least five medications the risk of adverse drug interactions increases up to 40% (1,2). Finally, for individuals taking at least seven medications the risk amounts to a disturbing 80% (1,2).

Hence, the risk of a toxic medication interaction is real considering that more than one half of non-institutionalized adults older than 65 years take five or more different medications, and 12% use ten or more medications (1,3). In the United States of America, among the hospitalized patients, adverse drug interactions are estimated to be as high as the fourth leading cause of death (1,4).

It has been convincingly demonstrated in the literature that toxic drug interactions can occur when two or more medications compete in such a way that their pharmacologic interaction causes a detrimental physiologic response (1). Alternatively, toxic drug interaction can occur when a medication is prescribed in excessive amounts, or when one medication produces inconvenient consequences although it is prescribed according to established guidelines (1). It has been argued that this last effect is often the most difficult to predict because drug absorption and metabolism can vary with age, concomitant illness, gastric motility, pH of the gastrointestinal milieu, genetic variation, smoking, or some other obscure physiologic parameter (1). On another aspect, it has been shown that the most dangerous drug combinations in the nursing home population involve warfarin interactions with non-steroidal anti-inflammatory drugs (NSAIDs), sulfonamides, macrolides, or quinolones; angiotensin-converting enzyme (ACE) inhibitor interactions with potassium supplements or spironolactone; digoxin interactions with amiodarone; and theophylline interactions with quinolones (1,5).

Descriptions of adverse drug reactions

According to the recent international literature, adverse drug reactions are described in Side Effects of Drugs Annual (SEDA) using two complementary systems, EIDOS and DoTS (6-8).

EIDOS

The EIDOS mechanistic description of adverse drug reactions consists of five components as briefly described below (6,9):

- *Extrinsic* species that initiates the reaction: this element may consist of the parent compound, an excipient, a contaminant or adulterant, a degradation product, or a derived product of any of these elements (e.g. a metabolite) (9).
- *Intrinsic* species affected: this element consists usually of the endogenous molecule interacting with the extrinsic species; it has been stated that this may include a nucleic acid, an enzyme, a receptor, an ion channel or transporter, or some other protein (9).
- *Distribution* of the species in the body: it has been shown that a drug cannot produce negative effects in the human body unless it is

distributed to the same site as the target species that mediates the respective adverse effects. Hence, it has been suggested that the pharmacokinetics of the extrinsic species may affect the incidence of adverse reactions in the organism (9).

- *Outcome* (either physiological or pathological): this consists of the adverse effect resulting from the interactions between extrinsic and intrinsic species. Physiological changes may consist of either increased actions (e.g. clotting due to tranexamic acid) or decreased actions (e.g. bradycardia due to beta-adrenoceptor antagonists). Pathological changes may consist of cellular adaptations (atrophy, hypertrophy, hyperplasia, metaplasia, and neoplasia), altered cell function (e.g. mast cell degranulation in IgE-mediated anaphylactic reactions), or cell damage (e.g. cell lysis, necrosis, or apoptosis) (9).
- *Sequela*, which is the adverse reaction of a given drug and may include several negative outcomes. These can be classified according to the Dose-Time-Susceptibility system (DoTS) (9).

Dose-Time-Susceptibility (DoTS) system

In the Dose-Time-Susceptibility (DoTS) system adverse drug reactions are described according to the *dose* at which they usually occur; the *timeline* during which they occur, and; the *susceptibility* factors that increase their likelihood, as briefly summarized below (7-9):

- *Dose*: relates to the toxic reactions (i.e. reactions which occur foe overdoses – alias supra-therapeutic doses); collateral reactions (which include reactions happening at normal therapeutic doses), and; hyper-susceptibility reactions (which consist of reactions happening even at low [sub-therapeutic] doses in particularly vulnerable/ susceptible individuals) (9).
- *Timeline*: reactions may be not related to the time of therapy (the so-called time-independent reactions which may happen at any given time during a certain therapy), or reactions may be fully contingent/dependent on the time of therapy (the so-called time-dependent reactions which include: immediate or rapid reactions, first-dose reactions, early tolerant and early persistent reactions, intermediate reactions, late reactions, withdrawal reactions, and delayed reactions) (9).
- *Susceptibility* (vulnerability) factors: include genetic predisposition, demographic characteristics (age and sex), physiological factors (such as e.g. weight, or pregnancy in women), exogenous factors (including lifestyle factors such as food habits, alcohol consumption, or smoking, as well as the effects of other drugs, devices, or surgical procedures), and presence of various diseases and conditions (9).

Situation in Kosovo including Gjilan region

The available information on drug interactions and their health effects for Kosovo is scarce. The anecdotic evidence though suggests a high prevalence of drug interactions and its resultant toxic effect. The situation is particularly problematic among the older population subgroup which is highly dependent on multiple drug use given the high prevalence of co-morbidity. The rapid socio-economic and political transition in the past two decades including the devastating war with Serbia has marginalized even more the older people in Kosovo. Indeed, the World Bank reports that Kosovo is among the poorest countries in Europe with older people being at a particularly high risk of poverty (10). The hard economic situation is also reflected in the poor health indicators of people in general and the older population subgroup in particular. This situation is particularly evident in Gjilan region. However, population-based data on drug use and misuse, drug interactions and their potential toxic effects are insufficient for Kosovo including Gjilan region.

Therefore, in the framework of information scarcity related to surveys and other studies focusing on drug interactions and their potential toxic effects in the population of Kosovo, there is

an obvious need to conduct population-based studies assessing the potential toxic effects of drug interactions in Kosovo, a post-war transitional country in the Western Balkans.

More specifically, there is a clear need to develop structured research protocols in order to assess the magnitude and determinants of drug interactions among adult men and women in Gjilan region and other parts of Kosovo using standardized and internationally validated instruments. The suggested study protocols should aim to assess the prevalence and predictors of drug interactions and their toxic effects among patients admitted to the hospital, but also among primary health care users in Kosovo.

Conflicts of interest: None declared.

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