

## CLINICAL SCIENCE

## USE OF DRUGS THAT ACT ON THE CYTOCHROME P450 SYSTEM IN THE ELDERLY

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**OBJECTIVES:** The objective of this study was to analyze medications that act on the cytochrome P450 (CYP450) enzymatic system and are used daily by non-institutionalized elderly individuals.

**METHODS:** A cross-sectional population-based study of elderly individuals ( $\geq 60$  years old) was conducted. All continuously used medications with hepatic metabolism via CYP450 that are classified as substrates, inducers or inhibitors were considered. For the analysis, elderly individuals were stratified according to age groups, and hepatic metabolism activity due to daily alcohol consumption and smoking were considered.

**RESULTS:** Elderly individuals (396 in total: 222 women and 174 men) between 60 and 95 years of age (mean: 72.1) were assessed. Use of drugs that act on CYP450 was identified in 61.6% of the subjects. Drug use was observed among 16.2% of the subjects: three drugs among 9.8% and four or more among 6.3% of the subjects. The metabolic activities of the drugs used were classified as substrates (58.8%), inhibitors (14.9%), and inducers (4.3%). The main drugs used were beta-blockers and statins (as substrates), proton pump inhibitors and fluoxetine (as inhibitors), and prednisone and carbamazepine (as inducers).

**CONCLUSIONS:** The results demonstrate that the elderly use high levels of medications that act on CYP450, thereby increasing the risk of drug interactions in a group that is already vulnerable to adverse drug effects.

**KEYWORDS:** Aged; Pharmacoepidemiology; Cytochrome P450; Drug utilization; Drug-drug interaction.

## INTRODUCTION

The elderly population presents high rates of morbidity, functional incapacity, and the use of multiple medications. These factors establish a higher prevalence of adverse drug reactions, most of which are due to polypharmacy and drug interactions.<sup>1</sup>

Drug interactions occur through concomitant use of drugs that can cause undesirable effects in the users. Pharmacokinetic and pharmacodynamic changes in the aging population establishes a higher vulnerability to drug interactions among the elderly.<sup>2,3</sup> This interaction

was identified in 44.5% of individuals in the geriatric population.<sup>4</sup>

Most pharmacokinetic interactions occur because of a drug's effect on the cytochrome P450 (CYP450) enzymatic system, in which drugs take on the roles of inhibitors, inducers, or substrates of metabolic activity.<sup>5</sup> There is genetic variability in the action of these enzymes, and this phenomenon may interfere with the patient's response to the use of certain medications.<sup>6</sup>

Some studies have observed frequent prescription of inappropriate medications among the geriatric populations.<sup>1,7,8</sup> However, despite the fact that elderly individuals represent a group with higher vulnerability to drug interactions, few authors have specifically analyzed the occurrence of this phenomenon among the elderly.

The present study was designed to identify the use of medications that may affect the CYP450 metabolism system among non-institutionalized elderly individuals by means of a home survey.

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## MATERIALS AND METHODS

*Study design:* A population-based cross-sectional analytical study

*Population and sampling:* Study subjects were individuals aged 60 years or more who were living in a district of the central region of the municipality of Londrina, Paraná, Brazil. The sample size was calculated using Epi-Info (StatCalc) software, considering a margin of error of 3%, a confidence interval of 95% and a possibility of losses of 20%. Selection of the elderly individuals was random with regard to the location of their homes, and the sample quotas were fulfilled in proportion to sex.

*Data collection:* The data were obtained by means of a home survey carried out by teams of trained researchers between June and August 2007.

### *Variables analyzed:*

- o Age – subjects were stratified into two groups for analysis: from 60 to 74 years of age and 75 years or over.
- o Sex.
- o Education level (years of study) – fewer than 4 years of study was used as the reference for a low education level.
- o Use of tobacco – only individuals who stated regular use of cigarettes at the time of the survey were considered as smokers.
- o Daily alcohol consumption – individuals were classified as presenting daily alcohol consumption if they reported any daily intake of alcoholic drinks, regardless of the volume consumed.
- o Use of medications that act on CYP450 – medications used regularly and continuously that act on any enzyme in the CYP450 system were recorded and classified according to whether they functioned as a substrate, inhibitor, or inducer of metabolism<sup>9</sup>.
- o Topical dermatological medications and medications not regularly used were excluded.

- o Botanical supplements that act on CYP450 such as St. John's wort were considered. However, none of the participants used such supplements.
- o Because of the activity of nicotine and alcohol on CYP450 (substrate and/or inducer), users of drugs with substrate or inducer activities were grouped together with smokers or individuals who reported a daily intake of alcoholic drinks<sup>9</sup>.

## Statistical analyses

The data were analyzed using Epi-Info software, version 3.4.1. The chi-squared test was used for frequency comparisons between the sexes and age groups. ANOVA was used to compare age means. The number of medications with activity on CYP450 and the type of activity on the system are presented according to age group. The significance level was set at 95%.

## Ethical issues

This project was approved by the research ethics committee of the State University of Londrina – Paraná – Brazil (number 261/06) in October 2006. Subjects signed a free and informed consent statement at the beginning of the interview.

## RESULTS

Three hundred and ninety-six elderly individuals ranging from 60 to 95 years of age (mean: 72.1 years) were assessed. Of these subjects, 222 were women (56.1%) and 174 were men (43.9%). Men presented higher frequencies of daily consumption of alcoholic drinks and the use of tobacco. There was no difference in the level of education frequencies between the sexes (Table 1).

The use of drugs that act on the CYP450 system was observed among 61.6% of the elderly individuals, and the proportion among women was higher (67.6%) (Table 1). The

**Table 1** - Characteristics of the population analyzed according to sex

| Variables                                | Total (396)<br>N ( % ) | Sex                   |                         | p-value |
|--|------------------------|-----------------------|-------------------------|---------|
|  |                        | Male (174)<br>N ( % ) | Female (222)<br>N ( % ) |         |
| Age in years (mean)                      | 72.1                   | 72.2                  | 72.0                    | 0.74*   |
| Low education level (< 4 years)          | 149 (37.6)             | 64 (36.8)             | 85 (38.3)               | 0.76    |
| Use of tobacco                           | 30 (7.6)               | 17 (9.8)              | 13 (5.9)                | 0.14    |
| Daily consumption of alcoholic drinks    | 33 (8.3)               | 31 (17.8)             | 2 (0.9)                 | < 0.000 |
| Use of drugs that act on Cytochrome P450 | 244 (61.6)             | 94 (54.0)             | 150 (67.6)              | 0.006   |

\* ANOVA

**Table 2** - Distribution of the number of drugs used that act on CYP450 according to age group

| Number of drugs that act on CYP450 | Total (396)<br>N (%) | Age group*                      |                                    |
|------------------------------------|----------------------|---------------------------------|------------------------------------|
|                                    |                      | 60 – 74 years<br>(240)<br>N (%) | 75 years or over<br>(156)<br>N (%) |
| 0                                  | 152 (38.4)           | 96 (40.0)                       | 56 (35.9)                          |
| 1                                  | 108 (27.3)           | 65 (27.1)                       | 43 (27.3)                          |
| 2                                  | 72 (18.2)            | 46 (19.2)                       | 26 (16.7)                          |
| 3                                  | 39 (9.8)             | 23 (9.6)                        | 16 (10.3)                          |
| 4                                  | 15 (3.8)             | 7 (2.9)                         | 8 (5.1)                            |
| 5                                  | 9 (2.3)              | 3 (1.3)                         | 6 (3.8)                            |
| 6                                  | 1 (0.3)              | 0 (0.0)                         | 1 (0.6)                            |

\*p = 0.3

use of more than two drugs that act on CYP450 was recorded among 64 individuals (16.2%) (Table 2).

Drugs with substrate activity formed the most frequently used group (58.8%). This proportion became 66.9% when the elderly individuals who smoked and/or consumed daily alcoholic drinks were grouped into this category. The use of drugs with inhibitor activity on CYP450 was observed among 14.9% of the subjects. Only 4.3% of the subjects used drugs with inducer activity. The frequency of participants that used drugs with inducer activity and/or consumed alcoholic drinks on a daily basis was 18.2%. There was no difference in the profile of drugs used between the two age groups (Table 3).

Among the drugs classified as substrates, the most frequently used were beta-blockers and statins. Proton pump inhibitors were considered as both substrates and inhibitors. In addition to these, the other inhibitors identified were the antidepressants fluoxetine and paroxetine. The most frequently used inducers were prednisone and carbamazepine (Table 4).

## DISCUSSION

The results demonstrate that the elderly individuals

assessed in the present study used a high number of medications that act on the CYP450 system. Most of the active drugs were classified as substrates, but some subjects also used drugs that were potential inhibitors and inducers.

In formulating geriatric prescriptions, it is very important to understand the effect of each drug on the CYP450 system, as drug interactions may enhance or reduce the drug's activity while increasing adverse effects.

This population-based study made it possible to analyze a representative group of non-institutionalized elderly individuals who frequently receive medical prescriptions for a wide variety of reasons.

Most (61.4%) of the elderly individuals analyzed used at least one drug that acted on CYP450, representing a higher potential for drug interactions.

Some authors have already demonstrated the importance of these medications for the elderly population, and have observed an increase in the use of medications that carry a potential risk of drug interactions.<sup>10</sup> In a previous study, 46% of geriatric patients were treated with at least one drug that is metabolized by CYP450.<sup>11</sup> In another study of individuals with a history of stroke, Classen et al. observed that 60% to 80% of these patients were using drugs that carry a risk of adverse interactions.<sup>12</sup>

It is important to emphasize that in the present analysis, medications were only considered if they had been used continuously, although sporadic use may also play an important role in drug interactions. Furthermore, this study did not analyze the specific enzymatic activity of the drugs, and thus it was possible that an individual may use two or more drugs that act on the CYP450, but via different enzymes. Such a situation would not represent a risk for drug interaction.

Another important factor for the risk of drug interactions (that was not analyzed in the present study) is the possibility of polymorphisms that give rise to a pharmacogenetic characteristic for users of the medication.<sup>13</sup> Despite the fact that genetic variability is an important determinant of enzymatic activity, racial factors could not be assessed due to the multiracial Brazilian population.

**Table 3** - Distribution of the drugs used according to the type of activity exerted on the CYP450 system and the age group

| Type of activity on CYP450                                  | Total (396)<br>N (%) | Age group                    |                                 | p-value |
|---|----------------------|------------------------------|---------------------------------|---------|
|   |                      | 60 – 74 years<br>(240) N (%) | 75 years or over<br>(156) N (%) |         |
| Substrate   | 233 (58.8)           | 138 (57.5)                   | 95 (60.9)                       | 0.50    |
| Substrate and/or smoker and/or daily consumption of alcohol | 265 (66.9)           | 163 (67.9)                   | 102 (65.4)                      | 0.67    |
| Metabolism inhibitor  | 59 (14.9)            | 32 (13.3)                    | 27 (17.3)                       | 0.27    |
| Metabolism inducer  | 17 (4.3)             | 10 (4.2)                     | 7 (4.5)                         | 0.88    |
| Inducer and/or smoker and/or daily consumption of alcohol   | 72 (18.2)            | 48 (20.0)                    | 24 (15.4)                       | 0.24    |

**Table 4 - Drugs used according to their action on the CYP450 system**

| Drug                                 | N (%)     |
|--------------------------------------|-----------|
| <b>Substrates</b>                    |           |
| Beta-adrenergic blockers             | 85 (21.5) |
| Statins                              | 77 (19.4) |
| Angiotensin II receptor blockers     | 48 (12.1) |
| Calcium channel blockers             | 28 (7.1)  |
| Benzodiazepines                      | 27 (6.8)  |
| Proton pump inhibitors               | 25 (6.3)  |
| Nonsteroidal anti-inflammatory drugs | 24 (6.1)  |
| Paracetamol                          | 18 (4.6)  |
| Tricyclic antidepressants            | 11 (2.8)  |
| Antihistamines                       | 5 (1.3)   |
| Warfarin                             | 4 (1.0)   |
| Glitazones                           | 3 (0.8)   |
| Cyclobenzaprine                      | 2 (0.5)   |
| Antipsychotics                       | 2 (0.5)   |
| Phenytoin                            | 2 (0.5)   |
| Lamotrigine                          | 1 (0.3)   |
| Zolpidem                             | 1 (0.3)   |
| <b>Inhibitors</b>                    |           |
| Proton pump inhibitors               | 25 (6.3)  |
| Fluoxetine                           | 16 (4.0)  |
| Paroxetine                           | 7 (1.8)   |
| Ticlopidine                          | 6 (1.5)   |
| Amiodarone                           | 5 (1.3)   |
| Fluvoxamine                          | 1 (0.3)   |
| Venlafaxine                          | 1 (0.3)   |
| Griseofulvin                         | 1 (0.3)   |
| Fluconazole                          | 1 (0.3)   |
| <b>Inducers</b>                      |           |
| Prednisone                           | 7 (1.8)   |
| Carbamazepine                        | 5 (1.3)   |
| Phenobarbital                        | 3 (0.8)   |
| Phenytoin                            | 2 (0.5)   |
| Rifampin                             | 1 (0.3)   |

In addition to inter-individual variability, frailty and age-related changes in pharmacology must be considered when adverse drug events are assessed in the elderly.<sup>14</sup>

Our data revealed that elderly women used more CYP450-active drugs than men, and represented a higher risk for adverse drug events. Moreover, some sex differences in pharmacology (renal clearance, volume distribution, and CYP450 activity) were found to increase the female risk.<sup>15</sup>

There were no differences in the number of drugs

used between the two age groups, but the group of elderly individuals aged 75 years or more may present a higher risk of drug interaction than that shown by the individuals aged 60 to 75 years. As people age, their hepatic metabolism rate changes, which increases elderly individuals' vulnerability to drugs that act on CYP450. Moreover, greater use of such medications and a higher prevalence of comorbidities, which contribute to the increased risk of adverse drug effects, were observed.<sup>16</sup>

Comorbidity represents a point of vulnerability among geriatric patients. Hepatic metabolism changes in disease states that are frequently observed in elderly patients, such as hypertension, diabetes, and obesity. In general, these patients possess low enzymatic activity due to their diseases, thereby increasing the risk of adverse effects.<sup>17</sup>

Approximately one third of the elderly individuals examined used two or more drugs that acted on CYP450, thus representing a potential drug complication. Johnell and Klarin studied elderly individuals (aged 75 years or over), and found a notable association between the number of drugs used and the risk of serious drug interactions in this population.<sup>18</sup>

Many drugs that are frequently used during day-to-day clinical practice are metabolized by the CYP450 system, and are classified as substrates. These drugs include antihypertensive drugs (beta-adrenergic blockers, Angiotensin II receptor blockers, and calcium channel blockers) and statins, which present evidence of benefits in clinical practice. Therefore, their use should be encouraged, despite the higher risk of drug interactions. However, we identified the use of drugs such as benzodiazepines, antihistamines, non-hormonal anti-inflammatory drugs, and tricyclic antidepressants, which not only represent a risk of drug interaction, but also are considered inappropriate for elderly due to their toxicity or low efficiency.<sup>19,20</sup> The frequency of benzodiazepine use was higher than that observed by other authors in both Brazil<sup>21,22</sup> and European countries.<sup>23</sup>

Among the group of subjects who used drugs with inhibitor activity on CYP450, use of the antidepressants fluoxetine and paroxetine must be highlighted. These medications present an unfavorable metabolic profile for the elderly population and a greater risk of serotonergic syndrome.<sup>24</sup> Nevertheless, they are commonly used among this population because of their lower costs.

Proton pump inhibitors present a wide range of activities on CYP450 and are currently widely used in clinical practice. Those who prescribe these drugs must consider the metabolic characteristics of the other medications in use, thereby minimizing the risk of a drug interaction.

Anti-convulsants (carbamazepine, phenobarbital, and phenytoin) and prednisone were the drugs that act on

CYP450 as inducers used by the elderly individuals studied. The inducing action may result in a lower efficiency of other concomitantly used medications, or of the production of toxic metabolites.<sup>9,25</sup>

Although a potential drug-herb interaction may occur due to the inducer action of St. John's wort,<sup>26</sup> the use of herbal preparations was not observed in this population. Social and cultural characteristics of the population and conditions of the local health service could account for this.

In addition to the metabolic activity of the drugs used, the effect of nicotine and alcohol on CYP450 was also considered in this analysis. The possibility of substrate activity increased from 58.8% to 66.9% when individuals who smoked and consumed daily quantities of alcohol were also included. The use of inducers increased from 4.3% to 18.2% when the consumption of alcohol or use of tobacco was taken into account. In medical practice, the possibilities for pharmacological interference due to the use of tobacco and alcohol must be kept in mind, in addition

to the well-known and disseminated problems related to health maintenance that are caused by these two behavioral patterns.

The data presented herein draw attention to the possibility of drug interactions in elderly patients that may be caused by the use of drugs that act on the CYP 450 system. The need for a better understanding of the activity pattern of drugs that are important in clinical practice and for knowledge of the determinants of adverse effects from these drugs is necessary when prescribing medication for the elderly.<sup>27</sup> Some authors have shown that careful evaluation of drug regimes resulted in a reduction of the adverse effects observed in geriatric outpatients taking more than one drug<sup>4</sup>, and reduced preventable prescribing errors by 13% in older patients<sup>28</sup>

Therefore, with respect to medical care of the elderly, the use of medications metabolized by the CYP450 system must follow the risk and benefit criteria that are pertinent to this age group.

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