Drug interactions in an elderly population
Prospective assessment of their frequency and severity among 56 patients

Summary

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Objective To assess the nature and the number of potential adverse drug interactions by analysis of outpatient prescriptions for elderly patients, of medications taken during the week before hospitalization in a general surgery department.

Method The study of 56 patients older than 65 years was conducted from November 2002 through February 2003. The outpatient prescriptions corresponding to medications taken during the 7 days before admission were analyzed by a pharmacy resident, who used data-processing tools and databases.

Results Most patients (83%) knew the reason for their prescription. Thirteen (28%) reported using over-the-counter medication. Only 89% of the patients reported complete compliance with the prescription. The average age of the patients was 72.1 ± 6.3 years and the median was 71 years [65-91]; 43% were women and 57% men. The 257 lines of prescriptions analyzed averaged 5.7 ± 2.6 drugs (range: 2-10) per prescription. The average number of possible interactions was 3.1 ± 2.8 per prescription for a total of 89 listed potential interactions. The levels observed were 3 warnings (3%), 37 precautions (42%) and 49 possible adverse interactions (55%). No contraindication was noted. The drugs mentioned most often were benzodiazepines, diuretics, conversion enzyme inhibitors, angiotensin II inhibitors, and beta-blockers. The potential risks most often found were hypotension, depression of the central nervous system, hypoglycemia and acute renal failure. The drug interactions were mainly due to the accumulation of the effects of separate drug classes. Deterioration in renal function was often noted as plasma concentration of the second drug increased.

Discussion This exploratory study shows the reality of the iatrogenic risk for elderly patients. This analysis of outpatient prescriptions is consistent with findings in the literature. Analysis of interactions is conducted on a pairwise basis. It is thus difficult to envisage the consequences of the association of 5 or more drugs in patients with complex illnesses and diminished physiological and metabolic capacity. Patient files kept by the pharmacist could provide information about individual combinations of the prescription and over-the-counter drugs.

According to Insee (the French statistics institute), persons older than 65 years accounted for 16% of the French population in January 2004. Roughly half were aged 65-74 years, and a little more than a third 75-84 years. The progressive aging of the population entails an increase in the frequency of chronic diseases and medication consumption, both of which increase with age. The frequency of complex multiple disorders among the elderly often leads to the use of multiple medications, relating to both doctors’ prescriptions and self-medication. Consumption of many drugs increases the likelihood of iatrogenic incidents, since each drug has its own risks and may also interfere with each of the others. The incidence of adverse effects is proportional to the number of drugs taken and increases with the duration of use. Nearly 5% of hospital admissions and more than 30% of iatrogenic disorders may be attributable to drug interactions. Surveys show that many prescriptions contain drugs incompatible with one another or dangerous for the elderly. Complications associated with medication use rank fifth on the list of causes of death in the United States. Pharmacists play an essential role in screening for risky drug combinations. They serve as a relay between patients, prescrip-
tions, and drugs. Studies show that pharmacists’ advice can reduce hospital admissions and improve quality of life, drug costs, and mortality\textsuperscript{10,11}.

We assessed the type and number of potential drug interactions through pharmaceutical analysis of the outpatient prescriptions of patients older than 65 years admitted to our general surgery department.

**Methods**

This four-month prospective study (November 2002 through February 2003) looked at 56 patients older than 65 years hospitalized in the general surgery ward of Jean Verdier Hospital (in Bondy, a town in the Paris metropolitan region). We studied the outpatient prescriptions by private practitioners – specifically, the drugs taken during the 7 days before admission. We did not take into account treatments begun or modified during hospitalization. Data came from the anesthesia consultation, prescriptions written by private practitioners, the medical and nursing records, and an interview of the patient by the pharmacy resident.

The resident then completed a form for each patient, listing the drugs, treatment adherence, and self-medication, as well as the patient’s knowledge about the drug. During the interview, the resident assessed knowledge, treatment adherence, and self-medication. The resident also analyzed each prescription with the Thériaque database\textsuperscript{12}, which provided immediate information about drug interactions, their severity, and the biological mechanisms involved, as well as the relevant bibliographic references. The database has been validated by the working group for drug interactions (GTIAM) of the French drug agency (Afssaps). It defines four levels of possible interactions:

- combination contraindicated because the clinical consequences are serious and frequent; this is an absolute contraindication;
- combination warned against, or a relative contraindication – should be avoided except for appropriate use in specific situations;
- precautions for use, where the combination is possible if guidelines are followed;
- “possible adverse interactions” for combinations in which a risk of interaction exists, but which can be used if supported by the physician’s assessment of the benefit/risk ratio.

**Results**

The patients’ mean age was 72.1 ± 6.3 years and the median 71 years (65-91). The sex ratio was uneven: 43% women and 57% men, a percentage consistent with that of the overall department patient population for all ages.

Eighty percent of the subjects lived with family members and 20% alone; none lived in an institution. Only 15% of the outpatient prescriptions had been included in the patient records. Prescription data were instead obtained mainly by the anesthetist during the preoperative consultation. During the interviews with the pharmacy resident, 28% of the patients reported self-medication.

The study analyzed 257 lines of prescriptions. The mean number of drugs on each prescription was 5.7 ± 2.6, with a range from 2 to 10. The mean number of possible drug interactions was 3.1 ± 2.8 per prescription for a total of 89 interactions identified. There were 3 potential interactions involving warnings (3%), 37 precautions (42%) and 49 possible adverse reactions (55%). No contraindication was observed. Table 1 summarizes for each level the principal possible clinical consequences and the nature of drug interactions. The most frequently mentioned drugs were benzodiazepines, diuretics, ACE inhibitors, ARBs, and beta-blockers. The most common potential risks were hypertension, depression of the central nervous system, hypoglycemia, and acute renal failure. Low blood pressure resulting from the combination of a diuretic and an antihypertensive (such as ACE inhibitors) is, of course, an interaction to be monitored, but is also intentional, since the combination is intended mainly for the treatment of hypertension. The other possible clinical effects of drug interactions, however, were really unwanted.

The interactions observed were mainly due to additive effects within a given drug class. This was the case for combinations that could cause low blood pressure or CNS depression. Effects on renal function were often observed with the increase of blood levels of combined drugs, including especially nonsteroidal antiinflammatory drugs (NSAIDS). The other drugs involved in interactions are detailed in Table 2.

Overall, 83% of the patients knew why they were taking their prescription. Thirteen (28%) patients reported taking medication on their own (self-medication). Only 89% of the patients reported adhering to the doctor’s prescription in every detail.

**Discussion**

This prospective analysis of outpatient prescriptions by private practitioners for patients older than 65 years showed that potential drug interactions were frequent, but their level of severity limited. The mean number of medications prescribed was similar to that in the literature, which ranges from 4.2 to 6.2. The Paquid study showed that the elderly living at home take an average of 4.5 different drugs per day and those in institutions 5.2\textsuperscript{13}. It reported that 43% of the patients took 5-10 drugs and 2.3% more than 10 a day. A study of 1500
<table>
<thead>
<tr>
<th>Clinical consequences (number DI/89)</th>
<th>Drug classes involved</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARNINGS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Hyperkalemia (2)                  | Potassium salts + ACE inhibitor  
ARB + hyperkalemic diuretic  | Decrease of circulating aldosterone leading to potassium retention |
| Hypoglycemia (14)                 | Hypoglycemic sulfa drug + cardioselective beta-blocker  
Hypoglycemic sulfa drug + noncardioselective beta-blocker  
Hypoglycemic sulfa drug + ACE inhibitor  
Hypoglycemic hormone + ACE inhibitor  
Hypoglycemic hormone + cardioselective beta-blocker  
Hypoglycemic hormone + NSAIDS | Action on pancreas cells, with increased risk of hypoglycemia  
Risk of hypoglycemia  
Elevated glucose tolerance with reduced needs for antidiabetic agents  
Mechanism not clearly established  
At strong NSAIDS doses, increased insulin secretion |
| Acute renal failure (6)           | NSAIDS + ARBs  
NSAIDS + antialdosterone  
NSAIDS + loop diuretic  
NSAIDS + ACE inhibitor  
ARBs + antialdosterone  
ACE inhibitor + ACE inhibitor + cardioselective beta-blocker | Decrease of glomerular filtration by NSAIDS  
Reduction of circulating aldosterone  
Additive effects of both classes |
| Hypotension (15)                  | ARBs + antialdosterone  
Cardioselective beta-blocker + ACE inhibitor  
Loop diuretic + ACE inhibitor  
Alpha-blocker + cardioselective beta-blocker  
Alpha-blocker + ACE inhibitor  
Calcium antagonist + phenothiazines  
Antihypertensive + hyperkalemic diuretic  
Imipramine + hypokalemic diuretic  
Imipramine + cardioselective beta-blocker  
Neuroleptic + hypokalemic diuretic  
Calcium antagonist + beta-blocker | Reduction in serum aldosterone level  
Additive antihypertensive effects  
Additive negative inotropic effects |
| Hypokalemia (2)                   | Loop diuretic + synthetic corticosteroid | Additive hypokalemic effects |
| Arrhythmia (4)                    | Digitalis + synthetic corticosteroid  
Digitalis + loop diuretic  
Antiarrhythmic agents + loop diuretic | Increased arrhythmogenic effects of digitalis  
Increased "torsade" effects due to the hypokalemia thus induced |
| Antagonism (1)                    | Synthetic corticosteroid + NSAIDS | Reduced salicylamia with risk of overdose if stopped suddenly  
The mechanism of this interaction is not well established |
| Rhabdomyolysis (1)                | Lipid lowering agent + Calcium antagonist | Reduction of hepatic metabolism of cholesterol-lowering agents |
| Low serum levels of thyroxine (1) | Thyroid hormone + anti-anemia agent | Decrease of digestive absorption of thyroxine |
| Hypertension (1)                  | Central antihypertensive + beta-blocker | If central antihypertensive stopped suddenly possible substantial increase in blood pressure |
| Acidosis (2)                      | Biguanides + ACE inhibitor | Diuretics may cause functional kidney failure in patients with diabetes, precipitating metformin-induced lactic acidosis |
| Central depression (34)           | Benzo diazepine + hypnotic  
Analgesic with morphine + benzo diazepine  
Analgesic with morphine + anticonvulsant  
Analgesic with morphine + hypnotic  
Benzodiazepine + antihistamine H1  
Anticonvulsant + hypnotic/Neuroleptic + anxiolytic  
Antihistamine H1 + hypnotic | Additive CNS depressive effects  
Additive adverse atropine-like effects |
| Reduced hypertensive effect (7)   | NSAIDS + cardioselective beta-blockers  
NSAIDS + non-cardioselective beta-blockers  
Synthetic corticosteroids + hypokalemic diuretics  
Cardioselective beta-blocker + NSAIDS  
Anti-glaucoma eye drops + NSAIDS | Antagonism of antihypertensive effect from corticoster  
oid-related water and salt retention  
 Vasodilatating prostaglandins inhibited by NSAIDS |

ACE: angiotensin conversion enzyme; ARB: angiotensin II receptor blockers; NSAID: nonsteroidal antiinflammatory drug.
prescriptions for subjects older than 65 years in the northeast regions found similar results\textsuperscript{14}. Psychotropic and cardiovascular drugs are mentioned most often in these studies. The frequency of potential drug interactions in our study (64%) was higher than that in the literature, which ranges from 27 to 60\%.\textsuperscript{6,15,16} The sample size may explain this difference. When we look only at the drug interactions validated by the GTIAM, those that are potentially dangerous, the prevalence of prescriptions at risk is on the order of 3.4\%. Nonetheless, less serious drug interactions must not be ignored; the elderly in particular are clinically vulnerable. The most frequent adverse effects are the risks of falls associated with orthostatic hypotension and confusional syndromes. The proportion of persons falling increases with age and leads to increased morbidity and even mortality among the elderly\textsuperscript{17,18}. Roughly one third of subjects aged 65 years or older fall at least once a year, and 5\% have fractures. In addition, 11-20\% of cases of mental confusion and delirium are thought to be drug-related\textsuperscript{19}. Falls are not the only harmful effect – the risks of cardiovascular disorders and hypoglycemia must also be considered.

This prospective study, although involving relatively few patients, points to a real iatrogenic risk for elderly patients. The data from the analysis of outpatient prescriptions by private practitioners are consistent with those observed in the literature. Knowledge of the pharmacokinetic and pharmacodynamic properties of drugs in the elderly should lead to improved dosing, if necessary. Improved management for the elderly requires implementation of appropriate clinical trials and systematic reporting of major adverse effects. Moreover, interactions are always analyzed on a pairwise basis, which makes it difficult to foresee the consequences of combining 5 or more drugs in patients with complex multiple disorders and compromised physiologic and metabolic capacities. The pharmaceutical analysis of prescriptions is thus helpful in assessing the potential risks of various drug combinations and treatment adherence. Patient files kept by the pharmacist could allow all information related to both prescriptions and over-the-counter drugs to be recorded.

Taking into account the pharmacokinetic and pharmacodynamic modifications associated with age, groups of geriatric researchers and pharmacologists have developed lists of the treatment classes and drugs whose prescription or use may be considered inappropriate among the very elderly. The consensus criteria most often used for improving prescription safety are the North American recommendations by Beers and the Canadian expert recommendations\textsuperscript{20,22}. Beers’s\textsuperscript{21} criteria pertain to those older than 65 years, whether they live at home or in an institution. They include 48 generic drugs, the prescription of which should generally be avoided. For example, NSAIDS in particular increase the risks of acute renal failure and hypertension, benzodiazepines the risk of falls and fractures. The criteria also point to specific drug risks in 20 particular illnesses: risk of increased hypoglycemia with dextropropoxyphene, increase in cognitive decline with benzodiazepines, and the sedative effect of muscle relaxants. These criteria have helped reduce the number of adverse effects from drugs prescribed for use at home\textsuperscript{20}.

**Conclusion**

Iatrogenic disorders remain frequent in geriatrics, especially those due to drug interactions\textsuperscript{23}. Prescribers must regularly assess treatment in the elderly to monitor adherence, efficacy, and tolerance, to adjust dosage and, if necessary, discontinue treatment. Clinical pharmacists can help this assessment.

The involvement of the pharmaceutical industry in setting up trials in this growing population group should help improve our knowledge about drug treatments.

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**Table 2**

**Other medications involved in drug interactions (DI)**

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>% DI per line of prescription</th>
<th>% DI per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>3.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>2.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Antianemia agents</td>
<td>0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Statins</td>
<td>0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Potassium salts</td>
<td>0.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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**WHAT IS ALREADY KNOWN**

- Iatrogenic risks are high among the elderly.
- A large number of drugs are prescribed on each prescription.

**WHAT THIS ARTICLE ADDS**

- Pharmaceutical analysis of outpatient prescriptions by private practitioners for patients subsequently hospitalized.
- Pharmacists’ activities in a surgical unit.
- Table of drug interactions according to therapeutic class.
- Specification of mechanisms of drug interactions.
References


