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Bleedings Induced by Oral Anticoagulants: a Study of Adverse Drug Reactions Reported to Midi-Pyrénées PharmacoVigilance Centre Between 2003 and 2006

Hémorragies induites par les anticoagulants oraux : une étude des effets indésirables notifiés au Centre Régional de PharmacoVigilance de Midi-Pyrénées entre 2003 et 2006

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1. Introduction

Bleeding is the major "serious" adverse drug reaction (ADR) of oral anticoagulants (vitamin K antagonists), drugs widely used in France (400 000 to 580 000 patients, *i.e.* around 1% of the total French population). Although the reported incidence of major bleeding episodes varies considerably, it is generally believed to be less than 5% per year in patients treated with a target of international normalized ratio (INR) of 2.0 to 3.0.[1] Moreover, several studies have shown that vitamin K antagonists are one of the leading drugs for inducing "serious" ADRs. For example, two French pharmacoepidemiological studies (performed at a 10 year interval) by the Regional PharmacoVigilance Centre Network found that vitamin K antagonists are among the most frequently drugs leading to hospitalization for ADRs.[2,3]

In the daily activity of the Midi-Pyrénées Pharmacovigilance Centre, reports of bleedings in patients treated by vitamin K antagonists are relatively frequent (more than 1 per week for many years). Thus, the present study was performed in order to describe the main characteristics of bleedings with vitamin K antagonists reported as ADRs to a Regional Centre of PharmacoVigilance in France.

2. Methods

The reporting of ADRs has been compulsory in France since 1984. According to the law, physicians must report "serious" or "unexpected" ADRs to their regional pharmacovigilance centre. All suspected ADRs are registered in the French PharmacoVigilance Database (FPVD).[4] For each report, information about patient (age, gender, medical history) and drug exposure (suspected and other associated non suspected drugs) are recorded in the FPVD. Causality assessment (imputation) is performed according to the French method used by all the regional centers of PharmacoVigilance.[5] A detailed summary of clinical description is added at the end of each pharmacovigilance case report. ADRs are coded according to ADR terminology of the World Health Organization (WHO-ART).[6–8] "Serious" ADRs were defined as reports leading to death, hospitalization (or prolongation of hospitalization), persistent or significant disability or incapacity, or being life threatening.[6–8]

All vitamin K related bleedings reported to Midi-Pyrénées PharmacoVigilance Centre between 1st January 2003 and 31st December 2006 and registered into the French PharmacoVigilance Database were included in the present retrospective study. For each observation, we recorded the main characteristics of patients (age, gender), drugs (Vitamin K antagonist, associated drugs), treated disease(s) and ADRs (localisation, "seriousness", evolution) as well as potential risk factors. Associated drugs were defined as all drugs taken by the patients in association with one vitamin K antagonist whereas drug interactions were selected as drugs listed by the summary of product characteristics (SPC) of the vitamin K antagonist.

Statistics were performed using univariate analysis. Results were shown as odds ratio (OR) with its 95% confidence interval.

3. Results

3.1. Descriptive analysis

Among the 5 277 notifications registered between 2003 and 2006 in the database of the Midi-Pyrénées PharmacoVigilance Centre, 195 (*i.e*. 3.7% with 98 men, mean age 76 years) were included in the study. Most of them (73%) included patients between 70 to 89 years.

Fluindione was the drug most frequently involved (151 cases). Acenocoumarol was used in 22 cases (11%) and warfarin in 21 (11%). The 3 main indications for oral anticoagulants were atrial fibrillation (n=62; 32%) followed by deep venous thrombosis (n=34; 17%) and cardiac valve (n=33; 17%). Localizations of reported bleedings were mainly cerebral (n=90; 47%) followed by subcutaneous (n=27; 14%), nasal (n=22; 11%), digestive (n=21; 11%), muscular (n=12; 6%) and urological (n=12; 6%).

This Vitamin K-associated ADR was lethal in 13% of cases (n=26). Recovery without sequela was found in 50% of cases (n=96).

INR values were higher than usually recommended in 45.7% of spontaneous notifications: values were between 4.5 and 8.89 in 26.8% of cases, between 9.0 and 19.99 in 14.6% and >20.0 in 4.3% of reports. INR values were lower than 2 in 11.6% of notifications.

The most frequent associated factors were age (85%), polymedication (51%), arterial hypertension (38%) and recent falls or traumatisms (26%). Drug associations were found in 62% of cases. The most frequently associated pharmacological classes were class 3 antiarrhythmics (amiodarone, n=37), statins (n=20), serotonin reuptake inhibitors (n=19) and thyroid hormones (n=17).

Drug interactions were involved in the hemorrhagic ADR in only 17.4% of cases. They belong to 3 main pharmacological classes: non steroidal anti-inflammatory agents (including aspirin), heparins and antibiotics (mainly beta lactamins and fluoroquinolones).

3.2. Statistical analysis

A statistical significant relationship was found between some associated factors and hemorrhagic localization: recent falls or traumatism and cerebral bleedings (p=0.00011), polymedication and nasal bleedings (p=0.007).

Moreover, evolution of cerebral bleedings was the more pejorative: OR death/recovery=12.96 (3.44-57.47).

In contrast, there was no significant association between presence of drug interaction and seriousness of ADRs, INR level and seriousness level, INR levels and ADRs evolution.

4. Conclusion

The present retrospective work was performed in order to precise the main clinical and pharmacological characteristics of bleedings related to Vitamin K antagonists reported to a Regional Pharmacovigilance Centre. Although the study suffers from some mandatory limits due to this kind of descriptive study using pharmacovigilance databases[7] (underreporting, selective reporting, lack of some informations in some reports, lack of data on total consumption…), it allows to underline some interesting pharmacological points.

First, bleedings with vitamin K antagonists is a relatively frequent reported ADR (around 4%) to Midi-Pyrénées PharmacoVigilance Centre. This result confirms the frequency and also the seriousness of this ADR, as previously described in numerous studies and, for example, the two pharmacoepidemiological studies on ADRs leading to hospitalization.[2,3] The present work also allows discussing the preventable character of this ADR since 43% of bleedings were observed in patients with too high values of INR.

As expected, this ADR was mainly observed in old patients treated with fluindione, the most used vitamin K antagonist in France. The importance of cerebral bleedings could be a bias of recruitment, since many of these ADRs' notifications came from anaesthesists working in the Neurosurgical Department of Toulouse University Hospital. Nevertheless, it underlines the seriousness of such localization since a clear association was found between risk of death and cerebral localization.

SPC listed several factors associated with the risk of bleedings with vitamin K antagonists. Among them, we found that age, polymedication, arterial hypertension and recent falls (or traumatisms) were the most frequently observed. Moreover, an interesting association between some of these factors and bleeding localization was found: recent falls (or traumatism) and cerebral bleedings, polymedication and nasal bleedings.

Drug interactions were involved in bleedings in 1 out of 6. This value underlines the importance of co prescriptions in the occurrence of such an ADR. Drugs involved in these interactions were not only agents well known to induce such an ADR with Vitamin K antagonists (aspirin or heparins), but also other drugs more neglected like beta-lactamins or fluoroquinolones.

In conclusion, the present pharmacovigilance study underlines some underestimated characteristics of this ADR, typically observed in polymedicated hypertensive old patients suffering from a recent fall or traumatism: seriousness of cerebral localization, lethal risk found in more than 1 patient out of 10, abnormal INR values 1 times out of 2 and drug association 1 times out of 6.

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