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Effect of Macrolide and Fluoroquinolone Antibacterials on the Risk of Ventricular Arrhythmia and Cardiac Arrest

An Observational Study in Italy Using Case-Control, Case-Crossover and Case-Time-Control Designs

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Abstract

Objective: To compare the effect of macrolide and fluoroquinolone antibacterials on the onset of ventricular arrhythmia and cardiac arrest using three different observational designs.

Methods: A population-based case-control study was performed by linking automated databases from the Varese Province of Italy. Cases were all subjects who experienced ventricular arrhythmia or cardiac arrest from July 1998 to December 2003. For each case, up to ten controls were randomly selected after matching for sex, age, practitioner and date of arrhythmia onset. The use of macrolides and fluoroquinolones during two time windows denoted as recent and referent intervals was ascertained. Odds ratios were estimated using case-control, case-crossover and case-time-control approaches.

Results: 1275 cases and 9189 controls met the inclusion criteria. Adjusted odds ratios (and corresponding 95% CIs) associated with recent exposure to macrolides were 2.13 (1.34, 3.39), 1.70 (0.88, 3.26) and 1.62 (0.78, 3.34) by using case-control, case-crossover and case-time-control designs, respectively. The corresponding estimates for fluoroquinolones were 3.58 (2.51, 5.12), 1.98 (1.19, 3.29) and 1.59 (0.88, 2.87), respectively.

Conclusions: Three observational study designs each using entirely different sets of controls consistently showed that recent use of macrolide and fluoroquinolone antibacterials may be associated with increased risk of ventricular arrhythmia and cardiac arrest.

Background

A variety of non-cardiovascular drugs (such as macrolide and fluoroquinolone antibacterials) may incidentally block potassium channels in myocardial cells, prolong the QT interval and trigger malignant arrhythmia.[1] Since severe arrhythmias are uncommon and unlikely to occur during pre-marketing trials, postmarketing surveillance based on formal observational designs would be the preferred way to detect such events. In spite of this, evidence supporting the role of macrolide and fluoroquinolone agents on the risk of arrhythmia is based on case reports, *in vivo* and *in vitro* non-clinical studies and on clinical investigations.[2] Conversely, although a very large number of patients receive such drugs, the impact of their use on the onset of arrhythmia at the population level has been investigated by only a few epidemiological studies.[3-8]

Observational studies of drug effects based on conventional designs are subject to important methodological limitations. Factors such as the tendency of certain individuals to have frequent contact with health systems (e.g. frequent physician contact and hypochondriacy), and the selective prescription of the drug of interest to patients with specific disease profiles are likely to affect the results of conventional pharmacoepidemiological investigations. As a consequence, the conclusion that there is no causal association might be reached.[9] Although statistical methods for correcting for the effects of confounders are widely available, computerized data derived from primary care or other automated databases only provides information on a limited number of potential confounding factors.[10]

For examining the effect of short transient exposures to drugs, and acute effects, Maclure[11] proposed the case-crossover design. The simple rationale of this approach is that the best control for each case is the case itself with, as reference, exposure data from another point in time. This overcomes the problem of between-person confounding by constant characteristics. More recently, Suissa[12] developed the case-time-control design, an extension of the case-crossover analysis that uses, in addition to the case series, a series of controls to adjust for exposure time trends. Although several studies have been published using these approaches in a variety of settings including pharmacoepidemiology, few in-depth empirical comparisons of these approaches have been performed.[13-16]

The aim of this large, population-based study was to assess the association of the use of macrolide and fluoroquinolone medications with the risk of ventricular arrhythmia and cardiac arrest, taking into account the effect of confounding, by comparing the estimates from three different observational study designs.

Methods

Target Population and Data Sources

The source population included all the residents of the Italian province of Varese, an area located between Milan and the Italy-Switzerland border. It comprises a population of nearly 700 000 residents aged 18 years or older according to the 2001 Italian population census. This population is entirely covered by the National Health Service (NHS), run since 1997 through a system of separate but electronically linkable databases including (i) the archive of residents who receive health assistance from the NHS (practically all the resident population), providing demographic and administrative data; (ii) the prescription drug database that contains information on all the drugs reimbursable by the NHS and dispensed at a regional level; (iii) the hospital discharge database that includes all admissions occurring in public and private hospitals; and (iv) the mortality database, holding death certificates of residents in the area. The privacy of patient records is ensured since no recognition key is present. However, a unique individual identification code (Regional Health Code) is consistently reported for all the databases to allow linkage among them.

Case and Control Selection

Cases were patients resident in the Varese area, aged 18 years or older, who from 1 July

1998 to 31 December 2003 experienced at least one event of ventricular arrhythmia or cardiac arrest. The date when each patient experienced the event (index date) was the earliest date among the first recorded date of (i) hospitalization or death with the following primary diagnoses, as coded by the *International Classification of Diseases*, 9th Revision (ICD-9): paroxysmal ventricular tachycardia (427.1), ventricular fibrillation and flutter (427.4), ventricular fibrillation (427.41), ventricular flutter (427.42), cardiac arrest (427.5), sudden death, cause unknown (798), instantaneous death (798.1); or (ii) death occurring in <24 hours from onset of symptoms, not otherwise explained (798.2) or unattended death (798.9). This outcome measure was found to have a positive predictive value of 73% compared with medical records.[17] In addition, prescription of mexiletine (Anatomical Therapeutic Chemical Classification System [ATC] code: C01BB02), the only anti-arrhythmic drug used for the treatment of severe ventricular arrhythmias,[18] was used to identify case patients who experienced ventricular arrhythmia during the study period.

Up to ten controls for each case were randomly selected from the residents in the province of Varese after matching for index date, sex, age and general practitioner who assisted the index case.

All eligible patients (cases and controls) who from 1 January 1997 to the index date were hospitalized for any form of cardiac dysrhythmia (ICD-9 code: 427) as a primary, secondary diagnosis or other relevant condition or to whom an anti-arrhythmic drug was dispensed (ATC code: C01B) were excluded.

Exposure Definition

All prescriptions of macrolide (ATC code: J01FA) and fluoroquinolone (ATC code: J01MA) antibacterials dispensed to each case and control from 1 January 1997 to the index date were extracted from the out-patient prescription drug database. The duration of all prescriptions dispensed to each patient was calculated by dividing the total amount of drug prescribed by the defined daily dose. For overlapping prescriptions, individuals were assumed to have refilled early and completed the first prescription before starting the second. Use of antibacterials during two periods, nominally the recent and referent time windows, was then considered. The recent time window was defined as the period immediately prior to the index date. The length of the recent time window was established as that maximizing the difference in prevalence of exposure to antibacterials among cases and controls. Starting from a minimum length of 4 weeks, we tested increments of 4 weeks up to 52 weeks. The referent time window was taken as 1 year prior to the index date extending back the same length of time as the recent time window.

Potential Confounders

Data on possible causes of arrhythmia such as exposure to other drugs and medical conditions were respectively gathered from prescription drug and hospital discharge records. The following conditions were considered: (i) use of other antibacterials (ATC code: J01 excluding J01FA and J01MA); (ii) use of antipsychotics (N05); (iii) use of antidepressants (N06); use of gastrointestinal prokinetics (A03FA); (iv) signs of heart disease supported by use of drugs for cardiac therapy (C01 excluding C01B) and/or hospitalization for ischaemic heart disease (ICD-9 codes: 410–414), disease of pulmonary circulation (415–417), and/or other forms of heart disease (420–429 excluding 427); (v) signs of other disease of the cardio-circulatory system supported by use of potassium-sparing diuretics (ATC codes: C03D and C03E), other diuretics (C03A, C03B and C03C), other drugs of the cardiovascular system (C02–C10 excluding C03), and/or hospitalization for other diseases of the circulatory system (ICD-9 codes: 390–459 excluding 410–429); (vi) signs of chronic obstructive pulmonary disease supported by use of drugs commonly used in its treatment (ATC codes: R03), and/or hospitalization for asthma or chronic obstructive pulmonary disease (ICD-9 codes: 490–496); and (vii) hospitalization for all other causes together. Exposure to each of these factors during the recent and referent time

windows was considered for case and control patients. The length of the recent time window was again established as that maximizing the difference in prevalence of exposure to each of these factors among cases and controls. The referent time window was defined by a period of the same length, but 1 year before the index date.

Data Analysis

Across all three study designs, conditional logistic regression for matched data was used to estimate the odds ratio, as an estimate of the rate ratio of the considered outcome, and 95% confidence intervals, associated with the recent use of macrolides and fluoroquinolones.[19]

Case-Control Design

First, the recent use of fluoroquinolone and macrolide antibacterials by each case patient during the recent time window was contrasted with the use of fluoroquinolone and macrolide antibacterials during the recent time window by the corresponding matched control and the corresponding odds ratio was denoted as a case-control estimate. To control for potential confounders, adjusted estimates were obtained by comparing cases and controls for the exposure to the above-reported factors.

Case-Crossover Design

Second, a case-crossover approach was used to estimate the odds ratio for recent exposure. The use of fluoroquinolone and macrolide antibacterials by each case patient during the recent time window was contrasted with the use of fluoroquinolone and macrolide antibacterials during the referent time window by the same case patient.[11] The corresponding odds ratio was denoted as a case-crossover estimate. To control for potential confounders, adjusted estimates were obtained by contrasting exposure to the above-reported factors of each case patient during the recent and referent time windows.

Case-Time-Control Design

Finally, a case-time-control design was implemented to control for exposure time trends.[12] This approach consisted of contrasting recent and referent exposure periods for case patients (the same set of patients considered in the case-crossover analysis), as well as for control subjects (those recruited according to the case-control design). By observing controls over time, a time trend of exposure in the source population was estimated through the control-crossover exposure odds ratio. Suissa[12] showed that the ratio between the case-crossover and the control-crossover exposure odds ratios produces an odds ratio adjusted for time trend. By assuming conditional independence of exposure within each matched set, a conditional logistic regression was fitted to estimate the time trend and the exposure effects. In particular, the effect of interest, nominally the one that measures the risk associated with drug exposure during the recent period with respect to referent time period in the case series (exactly as for the case-crossover design), was adjusted for the risk associated with the period effect measured in the controls. Further details of the case-time-control model are given in the original papers from Suissa.[12] To control for potential confounders, adjusted case-time-control estimates were obtained by contrasting exposures to the above-reported factors during recent and referent time windows within both case and control series.

For all tested hypotheses, two-tailed p-values less than 0.05 were considered to be significant.

Results

During the study period, 1275 cases and 9189 controls met the inclusion criteria and entered into the study. Cases were included because they were hospitalized for ventricular arrhythmia (n = 266) or cardiac arrest (n = 526), or because they died due to ventricular arrhythmia (n = 23), cardiac arrest (n = 306) or sudden death (n = 8) or because they had received mexiletine (n = 146). The mean age of case and control series was 70.2 years (standard deviation 17.6 years) and 48.5% were women (matching variables).

Table I gives the prevalence of exposure to the drugs of interest, as well as to other selected

Table I. Prevalence of exposure to macrolides, fluoroquinolones and selected potential confounders among cases and controls during two time windows. Province of Varese, Italy, 1998–2003

Factors	Cases (%) [n = 1275]		Control patients (%) [n = 9189]	
	recent time window[a]	referent time window[b]	recent time window[a]	referent time window[b]
Factors of interest				
Macrolides	2.7	1.3	0.8	0.9
Fluoroquinolones	5.1	2.3	1.1	0.9
Confounding factors				
Other antibacterials	21.3	15.9	11.0	10.1
Antipsychotics	0.9	0.8	0.4	0.4
Antidepressants	1.4	0.7	0.7	0.4
Gastrointestinal prokinetics	2.1	1.2	1.0	0.9
Heart disease	24.6	17.3	7.3	6.2
Other disease of cardio-circulatory system	54.4	46.3	33.7	31.2
Chronic obstructive pulmonary disease	13.7	10.7	5.6	4.9
Hospitalization for other cause	16.1	11.7	5.0	4.8

a The recent time window was 4 weeks before the index date for use of macrolides, fluoroquinolones, antipsychotics, antidepressants and gastrointestinal prokinetics, and 24 weeks before the index date for all the other factors.

b The referent time window was of same length delayed by 1 year with respect to the corresponding recent time window.

factors, in cases and controls during recent and referent time windows. A 4-week time window was calculated as that which maximized the difference in the prevalence of exposure to macrolides, fluoroquinolones, antipsychotics, antidepressants and gastrointestinal prokinetics between cases and controls. Conversely, a 24-week time interval was chosen as that which maximized the difference in prevalence of exposure between cases and controls for all other factors. The percentage of cases exposed to the drugs of interest during the recent time window was higher than that of cases during the referent time window and higher still when compared with controls during the same time window. Similar differences were observed for exposure to the other considered factors, especially for heart disease and hospitalizations. Controls showed a higher prevalence of exposure for almost all the considered factors during the recent time window than during the referent time window, suggesting a heterogeneous likelihood of exposure over the period of observation.

Table II presents crude and adjusted odds ratios for each of the three study designs. Both study design and adjustment of odds ratio affected the investigated effect. Compared with the case-control estimates, the odds ratios obtained from the case-crossover design, and those from the case-time-control approach, showed lower values. With the exception of the case-crossover effect of macrolides, adjusted estimates had consistently lower values than corresponding crude odds ratios. The adjusted case-crossover estimate for macrolides and the adjusted case-time-control estimate for both macrolides and fluoroquinolones did not demonstrate statistically significant evidence of association

Table II. Crude and adjusted effects of recent use of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest according to case-control, case-crossover and case-time-control designs. Province of Varese, Italy, 1998–2003

Study design	Macrolides OR (95% CI)	Fluoroquinolones OR (95% CI)
Case-control design		
Crude	2.66 (1.76, 4.03)	4.47 (3.20, 6.23)
Adjusted	2.13 (1.34, 3.39)	3.58 (2.51, 5.12)
Case-crossover design		
Crude	1.66 (0.92, 3.01)	2.50 (1.56, 4.01)
Adjusted	1.70 (0.88, 3.26)	1.98 (1.19, 3.29)
Case-time-control design		
Crude	2.05 (1.05, 4.00)	1.92 (1.10, 3.36)
Adjusted	1.62 (0.78, 3.34)	1.59 (0.88, 2.87)

OR = odds ratio.

with the risk of ventricular arrhythmia and cardiac arrest.

Discussion

In this study of subjects drawn from a large and well defined dynamic population, the recent use of macrolide and fluoroquinolone antibacterials appeared to be associated with an increased risk of ventricular arrhythmia and cardiac arrest. The increased risk was observed using three different approaches, namely case-control, case-crossover and case-time-control designs, each using entirely different sets of controls, and different procedures of adjustment of the estimates.

Comparison with Other Research

Our findings are consistent with those of other epidemiological studies. Some rare dysrhythmic events associated with the use of quinolones,[3] and both macrolides and fluoroquinolones,[6] possibly due to class effects, rather than to specific effects of a few drugs,[7] have been found by previous explorative investigations. A non-significant association between the use of fluoroquinolones and hospitalization for non-atrial cardiac arrhythmias has been found in a case-control study.[4] The rate of sudden death from cardiac causes among patients currently using erythromycin has been found to be almost twice that of patients who had not used antibacterial medications.[5]

Strengths and Limitations

The main strengths of the current study are the uniformly organized healthcare system allowing a large-scale population-based design, and the use of data on exposure and confounders that were collected before the onset of outcome. Thus, recall bias did not affect data collection.

The main weaknesses include potential information bias. Misclassification of included subjects according to their disease and exposure status due to errors in identification, diagnostic and therapeutic codings and uncertain compliance of patients with their treatment[20] might affect validity of the current estimates. Since misclassification of both diagnosis and exposure is expected to be non-differential, we expected that each of them will bias the estimates towards the unity. However, it is more difficult to predict their joint effect on the estimates.[21]

Despite the very large number of patients receiving the investigated drugs, statistical power considerations prevented the exploration of time windows shorter than 4 weeks. This may be considered inappropriate since a proarrhythmic effect is expected to arise a few hours after drug ingestion.[22,23] However, we recently reported an increased rate of arrhythmia at 15 weeks after discontinuation of fluoroquinolone, although with rates progressively decreasing.[8] A bias towards underestimation of the true effect can also be expected for this reason.

Comparing Study Designs

The main aim of our study is to compare estimates from different designs in order to take into account the effect of confounding.

Age and sex were matching variables in our case-control approach. Moreover, controls were selected among those assisted by the same general practitioner of each case patient in order to allow for physician behaviour in medication prescribing. Case-control estimates were furthermore adjusted for between-group differences in exposure to drugs and diseases known or suspected to cause arrhythmia. In spite of these precautions, case-control estimates should be interpreted with caution. Data on confounders such as co-morbidity, socio-economic status, lifestyle factors and individual behaviours are not fully captured in our study because they are not available in automated databases.[10]

The appeal of the case-crossover design is that within-subject comparisons avoid confounding by subject-specific attributes that are constant over time.[11] With respect to adjusted case-control estimates, the crude case-crossover estimates showed lower values. This suggests that between-person confounding by constant characteristics, including confounding by indication

as a common cause of bias in pharmacoepidemiology, was only partially controlled by the procedure of adjustment in the case-control approach.

However, because comparisons are made at different time periods, the validity of case-crossover estimates implicitly depends on the assumption that the distribution of the study exposure is stable over time. This is particularly problematic in our study because, owing to seasonal variability in the antibacterial utilization, a control period delayed by 1 year with respect to the recent time period was used.

Within-patient changes in certain conditions might have occurred over a so long an interval between the compared periods. An attempt to limit between-period confounding was made by adjusting the case-crossover estimates for changes in exposure to the same factors already considered for the case-control adjustment. A portion of the excess risk of arrhythmia associated with the recent use of fluoroquinolones was explained by changes in the exposure to these factors. Conversely, any relevant effect of the adjustment was observed for macrolides. However, residual confounding can not be excluded because between-period changes were likely not fully captured in our study.

Another key issue of case-crossover approach is the bias due to an inherent time trend in the prevalence of exposure. Changes in the market of antibacterials have occurred in the current setting with a reduction in macrolide prescriptions and increased marketing of fluoroquinolones. Changes over time can be incorporated with an extension of the case-crossover design, the case-time-control design as advocated by Suissa.[12] As expected, compared with crude case-crossover odds ratios, case-time-control estimates were increased for macrolides and reduced for fluoroquinolones. However, since these new estimates do not take into account changes in medical conditions over time, the case-time-control estimates were also adjusted for changes in exposure to the same factors already considered in the previous approaches. Again, a portion of the risk excess was explained by changes in the considered conditions, which occurred with different intensity in case and control series.

Adjusted case-time-control estimates did not offer statistically significant evidence of pro-arrhythmic potential for macrolides or fluoroquinolones. In general, due to an additional source of random error introduced by sampling the control group, the estimates based upon case-time-control approach are less efficient than those based upon a case-crossover approach, and the loss in efficiency is so much higher as exposure in the source population is rare. In our application, a 1% prevalence of antibacterial users was observed during the 4-week interval so that, even in our large study, the low statistical power limits the interpretation of not statistically significant, case-time-control estimates.

Interpretations

There are several possible explanations for the association of the use of antibacterials with the risk of arrhythmia.

First, infection itself might increase the risk of onset of ventricular arrhythmia and cardiac arrest, especially among patients with a history of cardiovascular disease. There is some evidence that acute infection increases the short-term risk of vascular events.[24] If such a possibility exists, the current findings might be accounted for, partly or wholly, by confounding due to indication.[25] At first sight this hypothesis seems to be confirmed by the observed important between-group, as well as between-period, differences in exposure to other antibacterials (table I). However, while a short-term effect of macrolides and fluoroquinolones was observed, the other antibacterials exerted more accentuated action for a longer period of 6 months. This suggests that exposure to other antibacterials might be interpreted as a proxy of the physician consultation frequency, rather than as reflecting the effect of antibacterials (or of the underlying infection) on the risk of arrhythmia.

Alternatively, macrolides and fluoroquinolones might be the direct cause of the considered adverse effect. It has been reported that drug-induced delay in cardiac repolarization favours the genesis of early after-depolarization, which can initiate an arrhythmia referred to as triggered activity.[26]

Additionally, the prolongation of QT interval by macrolides and fluoroquinolones, as well as by other proarrhythmic drugs, is often associated with increased heterogeneity of cardiac repolarization,[27] a substrate for a re-entrant mechanism responsible for the maintenance of arrhythmia. One particular type of arrhythmia, *torsade de pointes*, may cause syncope events and/or degenerate into ventricular fibrillation and death.

Detailed clinical information would be necessary to reach a definitive answer about the reason for excess of ventricular arrhythmia and cardiac arrest risk in patients in whom these antibacterials are prescribed.

Conclusions

Our findings suggest that current use of drugs belonging to antibacterial classes of fluoroquinolones and macrolides might be associated with increased risks of ventricular arrhythmia and cardiac arrest. The widespread use of these antibacterials highlights the importance of severe arrhythmic adverse effects as a clinical and public health issue. None of the three compared designs offer sufficient evidence on a causal role of macrolides and fluoroquinolones in the onset of severe arrhythmias. Both case-control and case-time-control approaches are vulnerable to confounding, including confounding by indication, but each in a different way.[28,29] The case-crossover design is not vulnerable to confounding by factors that remain constant within individuals, but to time trends in exposure or confounders. The case-time-control design, furthermore, generates less efficient estimates than other approaches. Thus, it may be prudent to use multiple designs whenever such a strategy seems warranted and economically feasible, as when using automated databases.

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