A study of the relation of exposure to quinolones and suicidal behaviour

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Aims To investigate the concern, raised by spontaneous reports received by the German regulatory authorities, that use of quinolone antibiotics may increase the risk for suicide and other suicidal behaviours.

Methods We carried out a nested case-control study using the General Practice Research Database (GPRD). We compared the risk of suicidal behaviours among users of quinolones, other antibiotics and no antibiotics.

Results From January 1, 1991 through April 30, 1995 we identified 348 cases of suicide, attempted suicide, or suicidal ideation and 808 controls. Compared with controls, cases who had received a prescription for a quinolone in the 30 days prior to the event had an adjusted relative risk (RR) estimate of 1.5 (95% CI 0.4–6.3) for any suicidal behaviour. Cases who had filled a prescription for a quinolone in the 31 to 180 days prior to their event had an adjusted RR estimate of 0.8 (95% CI 0.4–1.7) compared with controls. Cases who used other antibiotics in the 30 days prior to the event conferred an adjusted RR estimate of 1.1 (95% CI 0.6–2.2), and 0.9 (95% CI 0.6–1.3) for exposure in the 31 to 180 days prior to the event. The results were not materially different when suicide, suicide attempt, and suicidal ideation were analyzed separately.

Conclusions We conclude that there is no material increased risk of suicidal behaviours for use of quinolone antibiotics compared with non-use or use of other antibiotics.

Keywords: quinolone, suicide, case-control

Introduction

Reports to the spontaneous reporting system in Germany have raised concerns that exposure to quinolone antibiotics may increase the risk for suicidal behaviour, i.e., suicide, suicide attempt, and suicidal ideation. Some of the case reports described suicidal behaviour in quinolone users as long as 6 months after drug exposure. The current study was designed to compare the risk of suicidal behaviours among recent quinolone users with recent users of other antibiotics and people who had not recently received any antibiotic. We report on the results of a nested case-control study of people who had suicidal behaviour and a group of controls who did not have suicidal behaviour.

Methods

The study was based on information derived from the General Practice Research Database (GPRD). Since 1987, over four million residents in the United Kingdom have been enrolled with selected general practitioners (GPs) who use office computers provided by Value Added Medical Products (VAMP Health) and have agreed to provide data for research purposes to the GPRD which is currently owned by the United Kingdom Department of Health [1–3]. The GPs received 12 months of instruction on the

standardized recording of medical information and they agreed to supply *anonymized* information to academic researchers on an ongoing basis. The information recorded includes patient characteristics, drugs dispensed, clinical diagnoses, notation of referrals to consultants, hospitalizations, certain historical information and other findings, (e.g. smoking status, blood pressure, height and weight). Referral letters from consultants and hospitalizations are kept in a manual file. The general practitioners generate prescriptions directly from the computer, and these are automatically transcribed into the patient's computer record. The details of each prescription including dose, instructions and quantity are automatically recorded on computer and can be used to determine dose and duration of drug exposure. A modification of the Oxford Medical Information System (OXMIS) classification is used to enter medical diagnoses, and a coded drug dictionary based on the Prescription Pricing Authority's dictionary is used for the recording of prescriptions. (OXMIS codes were mapped onto ICD codes for the purpose of this study.) Two large validation studies determined that information on all patient referrals and hospitalizations present in the manual medical records in the general practitioners' offices was recorded on the computer over 90% of the time [1, 2].

Subjects

This was a case-control study. The base population from which the data were derived was restricted to subjects who

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used a quinolone antibiotic ($n=142\,316$) at some time between January 1, 1991 and April 30, 1995. The quinolones evaluated were ciprofloxacin, norfloxacin, ofloxacin, nalidixic acid, cinoxacin, enoxacin, acrosoxacin and temafloxacin. In order to be included, a subject had to have at least 18 months of information on drugs prescribed and diagnoses recorded on computer prior to the date of diagnosis. Subjects with a prior diagnosis of degenerative neurologic disease (i.e., stroke, multiple sclerosis), those with chronic liver or renal disease and those who were recorded as being drug addicts were excluded from the study.

Three groups of subjects aged 15–84 years of age were identified from the base population of quinolone users and formed the case groups: (1) persons who committed suicide (OXMIS code 3009D), (2) persons who had a diagnosis of attempted suicide (OXMIS codes L3009P, parasuicide; 9779L, drug overdose suicidal; and 3009C, attempted suicide) and (3) persons who had a diagnosis of suicidal ideation (OXMIS codes 3009BW, suicidal ideation; 3009BT, suicidal thoughts; and 3009BP, suicidal plans). If a subject had more than one of the 'case' diagnoses during the study period, only the first such diagnosis was considered. The index date from which exposure was determined was the date that the diagnosis was made.

Controls were derived from an initial random sample of 1000 subjects in the base population who did not have one of the 'case' diagnoses during the study period. The same exclusion criteria applied to cases were applied to the controls. A random index date between January 1, 1991 and April 1995 was assigned to each control subject and was considered to be the index date from which exposure was determined.

Exposures and covariates

The 'exposure window' was defined as the time from 180 days prior to the index date, to the index date, i.e., the date suicidal behaviour was first noted. In order to explore the effects of both short term and delayed effects we developed seven exposure categories. Exposure Group 1) quinolone use alone 1–30 days prior to the index date, Exposure Group 2) quinolone use alone in the 31–180 days prior to the index date, Exposure Group 3) single exposure to a non-quinolone antibiotic 1–30 days prior to the index date, Exposure Group 4) single exposure to a non-quinolone antibiotic 31–180 days prior to the index date, Exposure Group 5) multiple antibiotics *including* a quinolone in the 180 days prior to the index date, Exposure Group 6) multiple antibiotics *without* a quinolone in the 180 days prior to the index date and Exposure Group 7) no antibiotics prescribed in the period 1–180 days prior to the index date. For each subject we recorded: (1) age, (2) sex, (3) the indication for the antibiotic (if there was exposure), (4) a history of depression prior to the exposure window, (5) a history of suicidal behaviour (suicide attempt and/or suicidal ideation) *prior* to January 1, 1991, the starting date of the study, (6) a history of alcoholism, (7) history of treated epilepsy, (8) history of chronic treated insomnia, (9) history of chronic treated anxiety, and (10) history of prior diagnosis of treated psychosis.

Depression was considered in three levels: 1) Current

depression was defined as a diagnosis of *and* treatment for depression in the year prior to the exposure window, 2) other depression was defined as a diagnosis of depression, with or without treatment, *only* more than 1 year prior to the window of exposure, OR a diagnosis of depression within a year of the exposure window with no drug treatment, 3) No depression.

To be considered as having chronic insomnia or anxiety there had to be at least five events of diagnoses and/or prescriptions to treat the condition prior to the exposure window. A person was considered as having psychosis (schizophrenia, manic depressive disease, hallucinations, or delusions), or epilepsy if they had at least one diagnosis and one treatment for the condition prior to the exposure window. A subject was considered as an alcoholic, or as having a prior history of suicidal behaviour if there were any diagnoses for the conditions prior to the exposure window.

Analysis

Estimates of odds ratios for the various exposures under study were calculated using unconditional logistic regression with nonexposure to antibiotics (Exposure Group 7) as the reference group. Since the outcomes under study are rare, they approximate relative risks and are referred to as such. Analyses were carried out using SAS version 6.11 using the logistic procedure. Also the independent effects of each of the other variables were calculated.

Results

We identified 348 eligible cases of suicide, suicide attempt, or suicidal ideation and 808 controls. There were 13 cases of suicide, 206 cases of suicide attempt and 129 cases with suicidal ideation.

Table 1 provides the characteristics of cases and controls. Cases and controls were similar with respect to the indications for antibiotic use; 22% of cases and 23% of controls received the antibiotic for respiratory problems, 12% and 10% respectively for genitourinary problems, and 9% and 10% respectively for ENT problems. Cases, as compared with controls, were more likely to be female (76% and 64% respectively), young (25% of cases compared with 15% of controls were under the age of 30 years), and were more likely to have a history of depression, prior suicidal behaviours, chronic insomnia, or anxiety. In addition, cases were more likely to have a history of psychosis, alcoholism or epilepsy. The proportion of cases and controls not exposed to any antibiotic was similar—45% among cases and 49% among controls.

When relative risk estimates were calculated for all study outcomes combined, there were no material differences in risk across the different exposure groups compared with the nonexposed (Exposure Group 7). Table 2 provides the relative risk estimates (RRs) and 95% confidence intervals for this comparison both crude and adjusted for age, sex, and history of depression, suicidal behaviour, anxiety, insomnia, psychosis, alcoholism and epilepsy. The adjusted results did not materially differ from the crude results indicating that, whereas all of these risk factors were

Table 1 Characteristics cases and controls.

	Cases (%) n = 348	Controls (%) n = 808
<i>Sex</i>		
Female	263 (76)	522 (65)
Male	85 (24)	286 (35)
<i>Age (years)</i>		
<30	87 (25)	124 (15)
30–49	162 (47)	257 (32)
50–69	73 (21)	268 (33)
70+	26 (7)	159 (20)
<i>Antibiotic exposure</i>		
None	155 (45)	394 (49)
Quinolone 1–30 days	5 (1)	10 (1)
Quinolone 31–180 days	13 (4)	43 (5)
Other 1–30 days	22 (6)	49 (6)
Other 31–180 days	58 (17)	152 (19)
Multiple with quinolone	43 (12)	72 (9)
Multiple without quinolone	52 (15)	88 (11)
<i>Indication*</i>		
Respiratory	77 (22)	187 (23)
Genito-urinary	42 (12)	81 (10)
Ear, nose and throat	32 (9)	84 (10)
Other	42 (12)	62 (8)
<i>History of depression</i>		
None	166 (48)	696 (86)
Current prescription	145 (42)	61 (8)
Noncurrent	37 (11)	51 (6)
History previous suicide attempt	60 (17)	8 (1)
History chronic insomnia	22 (6)	18 (2)
History psychosis	15 (4)	4 (1)
History chronic anxiety	17 (5)	13 (2)
History of alcoholism	33 (9)	6 (1)
History of epilepsy	15 (4)	6 (1)

*No indication was present for the nonexposed.

independently associated with the study outcomes, they do not confound the relation between the study exposures and suicidal behaviour. The adjusted RRs for *all* outcomes combined were 1.5 (95% CI 0.4–6.3) for the quinolone 1–30 group compared with nonusers, 0.8 (95% CI 0.4–1.7) for the quinolone 31–180 group compared with non users, 1.1 (95% CI 0.6–2.2) for the other antibiotic 1–30 group, 0.9 (95% CI 0.6 to 1.3) for the other antibiotic 31–180 group, 1.3 (95% CI 0.8–2.2) for the multiple antibiotic with quinolone group and 1.1 for the multiple antibiotic use without quinolones group. These risk estimates were similar

when suicide attempt and suicidal ideation were analyzed separately.

No separate analyses were carried out for suicide as there were too few cases ($n=13$) to derive any meaningful results. There were no cases of suicide in users of quinolones in the 1 to 30 days prior to the index date.

For suicide attempt the adjusted RRs were 0.6 (95% CI 0.2–1.5), 1.2 (95% CI 0.5–2.6), 0.9 (95% CI 0.5–1.5), 1.2 (95% CI 0.6–2.2), and 1.0 (95% CI 0.5 to 1.8) for Exposure Groups 2 through 6 respectively. There were too few cases ($n=3$) exposed to quinolones alone in the 1 to 30 days prior to the index date to calculate a meaningful RR (Exposure Group 1). Table 3 provides these results, both crude and adjusted.

For suicidal ideation the adjusted RRs were 0.8 (95% CI 0.2–2.2), 0.9 (95% CI 0.3–2.5), 0.8 (95% CI 0.4–1.6), 1.4 (95% CI 0.7–2.9), and 1.1 (95% CI 0.5–2.2) for Exposure Groups 2 through 6 respectively compared with nonusers. There were too few cases ($n=2$) exposed to quinolones alone in the 1 to 30 days prior to the index date (Exposure Group 1) to calculate a meaningful RR. Table 4 presents the crude and adjusted results of these comparisons.

The independent effects of the covariates for *all* cases combined are presented in Table 5, adjusted for all other covariates simultaneously. Those with a prior history of depression, suicide attempt or ideation, insomnia, psychosis, alcoholism, or epilepsy were all at increased risk for one of the study outcomes and the risk decreased with increasing age. Males and females were at equal risk in these data. The RR for subjects with treated depression within the year prior to the index date was 9.0 (95% CI 6.1–13.4) compared with those with no depression, and 2.1 (95% CI 1.3–3.6) for people who had 'other' depression compared with those with no depression. The RR was 8.1 (95% CI 3.5–18.5) for people with a history of previous suicide attempt or suicidal ideation, 2.0 (95% CI 0.9–4.7) for people with chronic insomnia, 4.4 (95% CI 1.1–17.8) for people with psychosis, 1.6 (95% CI 0.6–4.0) for people with chronic anxiety, 9.2 (95% CI 3.3–25.2) for people with alcoholism, and 2.7 (95% CI 0.8–9.4) for people with epilepsy all compared to those without the condition. These results were all similar when analyzed separately by suicide attempt and suicidal ideation. The RR for females compared with males was 1.1 (95% CI 0.8–1.6). For ages 30 to 49, 50 to 69, and 70+ years, compared with age less than 30 years the RRs were 0.8 (95% CI 0.5–1.2), 0.3 (95% CI 0.2–0.5), and 0.2 (95% CI 0.1–0.3).

Table 2 Crude and adjusted RR estimates for all outcomes combined*.

Variable	Number of cases	Number of controls	Crude RR	95% CI	Adjusted RR	95% CI
Non-exposed**	155	394	1.0	—	1.0	—
Quinolone 1 to 30 days	5	10	1.3	0.4–3.8	1.5	0.4–6.3
Quinolone 31 to 180 days	13	43	0.8	0.4–1.5	0.8	0.4–1.7
Other antibiotics 1 to 30 days	22	49	1.1	0.7–2.0	1.1	0.6–2.2
Other antibiotics 31 to 180 days	58	152	1	0.7–1.4	0.9	0.6–1.3
Multiple antibiotics with quinolone	43	72	1.5	1.0–2.3	1.3	0.8–2.2
Multiple antibiotics without quinolone	52	88	1.5	1.0–2.2	1.1	0.6–1.7

*Adjusted for age, sex, history of depression, suicidal behaviours, insomnia, psychosis, anxiety, alcoholism, and epilepsy. **Reference group.

Variable	Number of cases	Crude RR	95% CI	Adjusted RR*	95% CI
Non-exposed**	91	1.0	—	1.0	—
Quinolone 1 to 30† days	3	—	—	—	—
Quinolone 31 to 180 days	6	0.6	0.3–1.5	0.6	0.2–1.5
Other antibiotics 1 to 30 days	14	1.2	0.7–2.3	1.2	0.5–2.6
Other antibiotics 31 to 180 days	36	1.0	0.7–1.6	0.9	0.5–1.5
Multiple antibiotics with quinolone	23	1.4	0.8–2.3	1.2	0.6–2.2
Multiple antibiotics without quinolone	33	1.6	1.0–2.6	1	0.5–1.8

*Adjusted for age, sex, history of depression, suicidal behaviours, insomnia, psychosis, anxiety, alcoholism, and epilepsy. **Reference group. †Number of cases too small to calculate adjusted RR.

Table 3 Crude and adjusted RRs for suicide attempt.

Exposure groups	Number of cases	Crude RR	95% CI	Adjusted RR*	95% CI
Non-exposed**	58	1.0	—	1.0	—
Quinolone 1 to 30† days	2	—	—	—	—
Quinolone 31 to 180 days	5	0.8	0.3–2.1	0.8	0.2–2.2
Other antibiotics 1 to 30 days	8	1.1	0.5–2.5	0.9	0.3–2.5
Other antibiotics 31 to 180 days	20	0.9	0.5–1.5	0.8	0.4–1.6
Multiple antibiotics with quinolone	18	1.7	0.9–3.1	1.4	0.7–2.9
Multiple antibiotics without quinolone	18	1.4	0.8–2.5	1.1	0.5–2.2

*Adjusted for age, sex, history of depression, suicidal behaviours, insomnia, psychosis, anxiety, alcoholism, and epilepsy. **Reference group. †Number of cases too small to calculate adjusted RR.

Table 4 Crude and adjusted RRs for suicidal ideation.

Table 5 Independent effects of the study covariates.

Variable	Adjusted RR	95% CI
Non-exposed*	1.0	—
Quinolone 1 to 30 days	1.5	0.4–6.3
Quinolone 31 to 180 days	0.8	0.4–1.07
Other antibiotic 1 to 30 days	1.1	0.6–2.2
Other antibiotic 31 to 180 days	0.9	0.6–1.3
Multiple antibiotics with quinolone	1.3	0.8–2.2
Multiple antibiotics without quinolone	1.1	0.6–1.7
Depression (current treated)	9.0	6.1–13.4
Other depression	2.1	1.3–3.6
Previous suicidal behaviour	8.1	3.5–18.5
Insomnia	2.0	0.9–4.7
Psychosis	4.4	1.1–17.8
Anxiety	1.6	0.7–4.0
Alcoholism	9.2	3.4–25.2
Epilepsy	2.7	0.8–9.4
Age 30–49 years**	0.8	0.5–1.2
Age 50–69 years	0.3	0.2–0.5
Age 70+ years	0.2	0.1–0.3
Female	1.1	0.8–1.6

*Reference group. **Compared with subjects <30 years of age.

Discussion

The current study using a case-control design evaluated the relationship of various antibiotic exposures to the risk of suicidal behaviour in subjects who received a quinolone antibiotic at some time during the period January 1991 to

April 1995. Various potential risk factors for suicidal behaviour were explored and adjusted for in deriving risk estimates.

In this study population of some 142 000 users of quinolone antibiotics there were only five subjects who developed suicidal behaviour within 1 to 30 days of a prior prescription for a quinolone antibiotic alone and only 13 subjects who developed suicidal behaviour in the 150-day period 31 to 180 days prior to a prescription. In a formal analysis of the results the frequency of such events after exposure to a quinolone antibiotic alone was found to be closely similar to the frequency after exposure to other antibiotics and after exposure to no antibiotic.

The results of this formal analysis show that exposure to any antibiotic compared with exposure to no antibiotic was not materially associated with the risk of developing suicidal behaviour in this population when either suicide, attempted suicide or suicidal ideation were the outcomes evaluated.

In particular, there was no material suggestion that quinolone antibiotics whether given alone or in combination with other antibiotics were associated with suicidal behaviour either in the 30 days after exposure or 31–180 days after exposure. The confidence intervals and the estimates are wide and we cannot rule out some effect. However, suicide is rare and necessarily leads to small numbers. Despite the small number of cases there is no suggestion of an effect of quinolones on the incidence of suicidal behaviours. A large number of potential confounding factors were measured and controlled for in the analysis and thus there is unlikely to be residual confounding by these factors.

As one might expect, we found that a history of

depression, previous suicidal behaviour, insomnia, psychosis, anxiety, alcoholism and epilepsy were associated with increased risks for suicidal behaviours. Age was inversely associated with suicidal behaviour; the risk decreased as age increased.

For this evaluation, we restricted the study population to subjects who used quinolones at some time during the period January 1991 to April 1995. From the findings it is apparent that other antibiotics were also used extensively in this population and that there were many periods of time when no antibiotics were prescribed. The use of a base population who were prescribed a quinolone antibiotic at some time during the study period not only increases the efficiency of the design, it also reduces the likelihood that selection bias related to the use of particular antibiotics influenced the results.

The quality of the data has been found to be high, but we cannot rule out some small amount of misclassification of exposure and outcome. However, there is no reason to believe that any misclassification would be differential.

This study describes data from the GPRD. There is no reason to expect that the results would not apply to the general population, but it is up to the reader to decide if experience in the UK can be applied elsewhere.

In summary, the current study provides evidence that antibiotics in general and quinolones in particular are not independently associated with an increased risk for suicidal behaviour.

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