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Telithromycin Use and Spontaneous Reports of Hepatotoxicity

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Abstract

Background and objective: Recent reports have described cases of telithromycin-related hepatotoxicity. The objective of this study is to quantify the effect of telithromycin use on the risk of hepatotoxicity.

Methods: We conducted a spontaneous-report case-control study of hepatotoxicity in telithromycin recipients using reports from the US FDA Adverse Event Reporting System. Reports from between 1 January 2005 and 30 June 2005 were examined. Cases included reports of patients with abnormal liver function tests, hepatocellular damage and hepatic impairment, while patients with reported conditions with similar reporting probabilities were considered as controls. The primary outcome measure of the analysis was the reporting odds ratio (ROR) evaluating the *a priori* hypothesis that telithromycin use confers an elevated risk of hepatotoxicity relative to other agents.

Results: A total of 2219 cases and 20 667 controls were identified. We estimated an ROR for hepatotoxicity associated with telithromycin compared with other agents of 1.82 (95% CI 1.12, 2.96) after controlling for age and gender, approximating an 82% excess risk in users of telithromycin relative to users of other agents.

Conclusions: This analysis is the first to specifically quantify the effect of telithromycin on the risk of hepatotoxicity. Telithromycin use may increase the risk of hepatotoxicity by >80%. Biases inherent in spontaneous reports include under-reporting of events and differential or time-varying reporting due to enhanced clinician awareness. Future studies should employ alternative data sources because of the inherent limitations of passive surveillance systems.

Background

Telithromycin was the first ketolide antibacterial to be approved in the US. It is indicated for the treatment of mild-to-moderate community-acquired pneumonia, acute bacterial sinusitis and acute bacterial exacerbation of chronic bronchitis.[1] Ketolides are semi-synthetic derivatives of macrolide antibacterials that were designed to have im-

proved antimicrobial activity and pharmacokinetics compared with the macrolides.[2]

On 29 June 2006, the US FDA announced changes to the product labelling for telithromycin to warn health practitioners and patients about the risk of hepatotoxicity.[3] They cited occurrences of serious liver injury and liver failure, along with four deaths and one liver transplant. Moreover, a recent case series by Clay and colleagues describes three cases of severe telithromycin-related hepatotoxicity.[4] Of these, one patient spontaneously recovered, one patient required orthotopic liver transplantation and one patient died. Autopsy reports from the deceased patient show hepatomegaly, substantial liver necrosis and evidence of a lymphocytic inflammatory response.[4]

The occurrence of telithromycin-related hepatotoxicity has been reported as being rare, although the precise incidence is unclear.[3] Phase III development programmes are generally underpowered to reliably detect rare events. Nevertheless, there was evidence of an increased risk of hepatotoxicity associated with telithromycin in comparative efficacy trials. Among the 11 reported trials that compared telithromycin with other antibacterials, six reported that hepatic adverse events were more common in the telithromycin group.[4] These trials included a total of 4870 participants, none of whom reported long-term hepatic impairment or death as a result of telithromycin use.

To our knowledge, no studies have been conducted with the specific aim of quantifying the effect of telithromycin use on the incidence of hepatotoxicity. Recent case reports serve as a signal of this potential adverse effect; however, the magnitude of increased risk is unclear. The objective of the current study is to quantify the effect of telithromycin on the occurrence of hepatotoxicity.

Methods

Study Design

We conducted a spontaneous-report case-control study using the FDA Adverse Event Reporting System (AERS) database. The AERS database consists of spontaneous reports from pharmaceutical manufacturers, healthcare providers and patients. Reporting is mandatory for pharmaceutical manufacturers, but voluntary for others. The AERS captures information on adverse drug and medical device events and product malfunctions. Adverse event reporters provide a description of the problem, including clinical outcome, relevant tests and the patient's medical history. The drug or product name and the dose and route of administration are reported for suspect medications, along with use of concomitant therapies. The extent to which some data elements are reported is limited. We ascertained drug exposure information from these reports. However, little information about the timing and duration of exposure and potential confounders was available. Furthermore, the onset of hepatotoxicity is generally idiosyncratic and we therefore had no *a priori* hypothesis about the necessary dose or duration of therapy with telithromycin that would be needed to cause hepatocellular damage. To inform the evaluation with regard to potential biases, we also estimated the effect of the use of any macrolide antibacterial on the reporting of hepatotoxicity. Macrolides are used in similar clinical settings to telithromycin and hepatotoxicity is recognised as a rare adverse effect associated with their use.[5] We used data from 1 January to 30 June 2005; this timeframe captures a period after the approval of telithromycin by the FDA and before the initial case reports of hepatotoxicity in the literature. Using the principles of spontaneous-report case-control studies as described by Rothman and colleagues,[6] we present an estimate of the risk ratio for the effect of telithromycin

on the risk of hepatotoxicity relative to other medications in the reporting system.

Selection of Cases and Controls

We selected reports of liver injury or hepatic impairment as cases. These included reports of elevated liver function tests, jaundice, hepatocellular damage and liver failure. We chose to use a broad definition of liver damage because there were insufficient data to enable restriction to overt impaired hepatic functioning within the specified timeframe. To decrease the likelihood of incorrectly overestimating the prevalence of telithromycin use in the control population, we selected control diagnoses that we considered to be unrelated to telithromycin exposure based on previous reports. Excluded conditions were diarrhoea, nausea, dizziness, vomiting and abdominal pain. These treatment-emergent adverse events are considered to be possibly related to study medication and were observed in ≥2% of patients in several clinical trials.[7-15] Furthermore, we selected control conditions thought to have a probability of being reported to the AERS database that was similar to that of hepatotoxicity in order to further decrease the probability of differential reporting bias. The included diagnoses vary slightly with regard to reporting probability, but we selected them to reflect the same average reporting probability as the cases. The control diagnoses included elevated blood creatinine levels, thrombocytopenia and deep vein thrombosis. Table I lists the conditions chosen to represent cases and controls. One author first selected a list of reported diagnoses for the cases and controls. Then, all authors met and discussed the list until agreement was reached about which to include. Reported diagnoses were coded as preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a common coding system used worldwide by pharmaceutical manufacturers and regulatory agencies, and was developed under the sponsorship of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[16]

Table I. Distribution of diagnoses selected as cases and controls[a] based on Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms

Diagnoses	Proportion of patients (%)
Cases	
Increases in hepatic enzyme levels	58.8
Elevated bilirubin level	5.9
Hepatic failure	9.9
Liver disorder	5.7
Jaundice	5.7
Abnormal hepatic function	4.3
Hepatocellular damage	5.8
Hepatic necrosis	1.2
Hepatitis toxic/hepatotoxicity	2.7
Controls[a]	
Gastrointestinal (e.g. abdominal pain, intestinal ischaemia)	8.1
Vascular/renal (e.g. hypertension, hyperkalaemia)	26.0
Pain/discomfort (e.g. back pain, extremity pain)	11.3
Haematological (e.g. agranulocytosis, leukopenia)	9.4
Dermatological (e.g. pruritus, application site pain)	3.3
Musculoskeletal (e.g. arthralgia, osteopenia)	4.9
Psychiatric/neurological (e.g. confusion, insomnia)	11.7
Respiratory (e.g. dyspnoea, painful respiration)	5.6
Other (e.g. drug exposure during pregnancy, asthenia)	19.6

a A detailed list of MedDRA preferred terms for controls is available from the authors.

Statistical Analyses

We calculated reporting odds ratios (RORs) and 95% confidence intervals; these estimates can be interpreted as relative risks. We present estimates stratified by age and gender and adjusted for differences in these parameters between the case and control group using Mantel and Haenszel's method.[17] Reliable measurement of other potential confounders is not available in the AERS because of incomplete reports. We conducted confirmatory multivariable logistic regression analyses, first modeling age continuously and then using discrete categories (18–44, 45–64 and ≥65 years of age). All

Table II. Stratified estimates of the effect of telithromycin and macrolides on the risk of hepatotoxicity compared with other drugs represented in the US FDA Adverse Event Reporting System database

Category	Cases (n)	Controls (n)	Telithromycin reporting odds ratio (95% CI)	Macrolides reporting odds ratio (95% CI)
Crude	2 219	20 667	1.91 (1.18, 3.09)	1.87 (1.36, 2.57)
Adjusted[a]	2 219	20 667	1.82 (1.12, 2.96)	1.85 (1.42, 2.42)
Age (y)				
18–44	579	4 840	1.55 (0.59, 4.05)	3.12 (1.69, 5.76)
45–64	918	7 798	2.28 (1.20, 4.33)	1.86 (1.07, 3.19)
≥65	722	8 029	1.28 (0.39, 4.25)	2.48 (1.52, 4.05)
Gender				
female	1 151	13 119	1.38 (0.63, 3.03)	2.17 (1.42, 3.32)
male	1 055	7 440	2.37 (1.26, 4.45)	1.53 (0.94, 2.49)

a Adjusted for age and gender using Mantel and Haenszel's method.[17]

analyses were conducted using SAS software, version 9.13 (Cary, NC, USA). The funding source had no role in the conduct of this study. The Brown University Human Research Protections Office determined this work was exempt from Institutional Review Board review because the data are de-identified and publicly available.

Results

The study sample consisted of 2219 cases and 20 667 controls. Overall, reports that included telithromycin were rare, with 20 exposed cases and 98 exposed controls. There were 46 macrolide-exposed cases and 231 macrolide-exposed controls. On average, the controls were more likely to be female (64% vs 52%) and aged >64 years (39% vs 33%). The results of the crude and stratified analyses are presented in table II. There were notable differences in the effect of telithromycin on risk of hepatotoxicity across categories of age. Furthermore, the risk appeared to be modified by male gender. The increase in risk of hepatotoxicity associated with telithromycin in men (ROR 2.37; 95% CI 1.26, 4.45) was nearly double that in women (ROR 1.38; 95% CI 0.63, 3.03). Similarly, individuals aged 45–64 years had greater increase in risk associated with telithromycin (ROR 2.28; 95% CI 1.20, 4.33) than those aged 18–44 years (ROR 1.55; 95% CI 0.59, 4.05) and those aged ≥65 years (ROR 1.28; 95% CI 0.39, 4.25). The use of macrolides was similarly associated with increased reporting of hepatotoxicity relative to other drugs in the AERS. As with telithromycin, there was marked heterogeneity within strata of age and sex. However, unlike telithromycin, the highest estimated increases in reporting risks were in women and among those aged 18–44 years. The results from the multivariable logistic regression models were consistent with those from the stratified analyses.

Discussion

We estimated an 82% increased risk of hepatotoxicity in users of telithromycin relative to users of other agents. We also estimated an 85% increase hepatotoxicity risk among users of macrolide antibacterials. These findings are consistent with current knowledge about the risk of liver injury associated with use of antibacterials.[5] The effect of telithromycin on the risk of hepatotoxicity was greater in men than in women. The current study could not estimate the absolute risk of hepatic injury owing to telithromycin, but the FDA acknowledges it is a rare occurrence.[3] Clay and colleagues reported that telithromycin-induced hepatotoxicity can lead to serious injury or death.[4] Thus, the impact of rare events may be substantial in light of the 3.35 million pre-

scriptions written for telithromycin in the US in 2005.[18] In the ongoing battle with drug-resistant bacteria, telithromycin has a secondary role to play in the prescriber's armamentarium, but physicians must be mindful of the potentially serious adverse effect of hepatotoxicity.

The risk of liver injury associated with telithromycin appeared to be more substantial in men than women. One plausible explanation is that the observed patterns reflect distortions due to uncontrolled confounding variables, such as paracetamol (acetaminophen) or alcohol use. Paracetamol use accounts for a large proportion of treated cases of liver failure.[19] Moreover, alcohol use is a strong, independent risk factor for liver injury.[20] Men are more likely than women to abuse or be dependent on alcohol.[21] These factors may account for the apparent differences in the risk of liver injury associated with telithromycin and gender. Concomitant use of alcohol and paracetamol may also explain the heterogeneity of the ROR across categories of age. Evidence suggests that alcohol use declines with age,[22] while paracetamol use increases.[23] In the present study, individuals aged 45–64 years may have been most likely to use both alcohol and paracetamol, while the other participants may have only taken one or the other. Alternatively, these results may reflect the presence of a biological interaction between telithromycin use and pre-existing liver damage, especially among alcohol users.[24] We need more data on comorbid conditions and prior exposures to make this distinction. The effect heterogeneity among users of macrolides is plausibly the result of similar influences, with the observed differences from the telithromycin group resulting from different distributions of confounding factors and effect modifiers.

Care must be taken in the communication of the risk of hepatotoxicity associated with telithromycin. The effectiveness of letters to healthcare providers regarding changes in safety-related information is limited[25,26] and may be due to deficiencies in wording of the letters.[27] A lack of regulatory action or an over-emphasis on the risk of an adverse effect may lead to the under-prescribing of a useful drug. Under-recognition of these risks may lead to unnecessary harm to patients.

The AERS data consist of spontaneously reported adverse events information and are thus subject to differential reporting biases.[28] Moreover, it is difficult to ascertain whether our control selection criteria lead to an accurate estimate of telithromycin use in the source population of the study. An inaccurate estimate of the prevalence can lead to spuriously increased or decreased RORs. Under-reporting is considered to occur frequently within the AERS, but relative over-reporting can occur after a drug has been linked to a particular adverse event in the literature, causing providers to become more cognisant of the potential adverse effect. Depending on the type of differential reporting, effect estimates can be either inflated or attenuated. This study addresses these concerns in several ways. First, to limit the effect of differential reporting bias on the validity of our study, we defined our observation period as beginning after the approval of telithromycin by the FDA and ending before the initial case reports of hepatotoxicity appeared in the literature. However, this does not rule out the possibility of heightened awareness as a result of hepatotoxicity signals in the phase III clinical trials of telithromycin. This influence may have increased the probability of reports related to telithromycin. This timeframe was not selected with the reporting probability of macrolide-related events in mind. The association of macrolide antibacterials with hepatotoxicity was long-established during the time period for which data were collected.[5] Second, we selected cases and controls with adverse events with similar reporting probabilities to decrease the likelihood of bias due to differential under-reporting. By choosing adverse events for the case and control series that are moderate to

severe in nature and plausibly related to medication use, the likelihood of differential under-reporting bias is minimised as the magnitude of under-reporting will be similar in the cases and controls. Third, we excluded diagnoses from consideration as control conditions if they were known to be related to telithromycin. This approach decreases the likelihood of overestimating the prevalence of exposure in the control group and biasing the effect estimate toward the null effect. These events are also known to be related to macrolide antibiotics and ensure a more accurate estimate of the prevalence its use. This methodology extends signal detection to provide a more valid estimate of the relative risk.[6]

Confounding by unmeasured factors was a concern in the present study. One possible approach to attenuate this potential bias would have been to restrict our analysis to users of antibacterials. We chose not to restrict our analysis in this manner because we conducted the study using case-control methods to deal with the potential for differential reporting bias and to address the inherent limitations of disporportionality analyses.[6] Because the AERS provides only limited data on concomitant medication use, it would have been difficult to sample the controls to represent the source population. This could have lead to an inaccurate estimate of the prevalence of use of telithromycin in the source population, which would have biased the ROR.

Spontaneous report data are further limited by insufficient information on potential confounders. Indeed, the spontaneous report forms ask for relevant medical history and concomitant medicine use; however, the majority of these data are missing. As a result, little can be done to directly rule out the possibility of relevant confounding.

Conclusions

Future studies on the risk of hepatotoxicity associated with telithromycin use are needed to further account for biases inherent in spontaneous report data and to identify populations at high risk. These studies should utilise alternative data sources and focus on demographic and clinical characteristics that may modify the effect of telithromycin on the risk of hepatotoxicity.

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