Torsades de pointes induced by antibiotics
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Abstract

Background: Several frequently used antibiotics are associated with an arrhythmia called “torsades de pointes” (TdP). This potentially fatal arrhythmia is considered unpredictable.

Methods: In order to investigate the prevalence of risk factors for TdP prior to initiation of antibiotic therapy, we conducted a literature search for all published reports on TdP induced by antibiotics and we asked pharmaceutical companies for additional unpublished reports.

Results: We studied 61 reports on 78 patients with TdP induced by antibiotics. Female gender was the most common risk factor for TdP: 66.7% (n=52) of all patients were women. Advanced heart disease and concomitant use of a QT interval-prolonging agent or an inhibitor of liver drug metabolism were also frequently present (59% and 48.7%, respectively). Most patients had at least one and 58 patients (74.3%) had two risk factors or more for TdP prior to initiation of antibiotic therapy.

Conclusion: Contrary to common belief, TdP induced by antibiotics may be predictable by simple history-taking and by obtaining a baseline electrocardiogram. We wish to draw attention to risk factors for TdP prior to the initiation of antibiotic therapy.

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1. Introduction

Torsades de pointes (TdP) is a rare form of arrhythmia that was first described in 1966 [1]. This potentially fatal arrhythmia is associated with congenital long-QT syndrome (LQTS) or with drug administration. Several anti-arrhythmic agents, such as quinidine (class IA), sotalol (class III) and bepridil (class IV), block specific potassium channels in the myocyte membrane, thus reducing an outward potassium current called $I_{Kr}$. The blockage of this major repolarizing potassium current participates in prolongation of the action potential in the ventricular myocardium and this leads to the clinical finding of QT interval prolongation [2]. Some patients might exhibit extensive prolongation of the QT interval while taking these drugs and they are at risk for TdP [3].

Like the above-mentioned anti-arrhythmic agents, virtually, all drugs that prolong the QT interval and cause TdP also block the potassium current $I_{Kr}$ [4]. Blockage of $I_{Kr}$ has been demonstrated in vitro by several antibiotics, and particularly by macrolides and quinolones [5–7]. Most macrolides and quinolones, including erythromycin, clarithromycin, roxithromycin, gatifloxacin, levofloxacin, moxifloxacin and sparofloxacin, have been associated with TdP in the clinical setting [8–58]. Other macrolides and quinolones, including azithromycin, troleandomycin and ciprofloxacin, have been clinically associated with TdP [59–62], probably by the same mechanism of blocking the potassium current $I_{Kr}$, although no laboratory experiments demonstrating this association are available. Trimethoprim–sulfamethoxazole and metronidazole have also been associated with TdP in several clinical reports [63–65], but the mechanism by which these drugs prolong the QT interval is not clear [66].

In a previous study, we analyzed 144 reports on 249 patients who had developed TdP while taking drugs for non-cardiac indications, i.e., antibiotics, antihistamines,
psychotropic drugs, etc. We looked for risk factors for TdP prior to the initiation of the offending drug, such as female gender, advanced heart disease, hypokalemia, high drug concentrations, concomitant use of a QT interval-prolonging agent and subclinical LQTS. The most commonly identified risk factor for TdP was female gender (71%); other risk factors for TdP were frequently present as well (18–41%). We then concluded that most patients with TdP induced by non-cardiac agents had had easily identifiable risk factors for TdP prior to initiation of the offending drug [67]. Several additional reports on TdP induced by antibiotics have been published since then, describing novel associations [49–51,53,61,62,65,68]. In this review, we turned our attention to the association between antibiotics and TdP. By using the above-mentioned database and these recent reports, we sought to define how often there had been identifiable risk factors for TdP prior to initiation of antibiotic therapy and TdP occurrence. In order to address internists, we studied additional risk factors for TdP that were not studied in the previous article but that might be relevant to daily practice in internal medicine, such as advanced age, intravenous administration of antibiotics, renal failure and congestive heart disease.

2. Materials and methods

2.1. Retrieval of reports

We performed an electronic literature search in PUBMED until September 2005 using the key words “QT interval”, “torsades de pointes”, “antibiotics”, “macrolides”, “quinolones” and “sudden death”. We then reviewed each of the original articles that had been mentioned on the Internet. The references in each of these reports were further reviewed for additional publications. We also asked pharmaceutical companies for data on patients who had developed TdP during clinical trials of new antibiotics. Bayer (Bayer Corporation, West Haven, CT, USA) provided data on three patients who had developed TdP while taking moxifloxacin. Bristol-Myers Squibb (Bristol-Myers Squibb Company, Princeton, NJ) provided data on seven patients who had developed TdP during the clinical evaluation of gatifloxacin.

2.2. Risk factors for torsades de pointes

Each case report was analyzed for the presence of risk factors for TdP that could have been easily identified prior to the initiation of antibiotic therapy. These risk factors included: (1) female gender [69] and middle-aged or older women in particular [2]; (2) advanced heart disease [2], particularly congestive heart failure [70]; (3) hypokalemia [71,72], defined as potassium serum levels below 3.5 meq/L; (4) digitalis therapy [73]; (5) concomitant use of a QT-prolonging agent [2] or an inhibitor of hepatic drug metabolism [74]; and (6) subclinical LQTS, defined as a family history of LQTS, a history of drug-induced TdP [75,76], a prolonged QT interval (QTc ≥ 450 ms) on the baseline electrocardiogram and congenital LQTS [76]. Several clinical features that had been associated with TdP were also taken into account, namely, intravenous administration of a QT interval-prolonging drug [77], the use of macrolides in the elderly [78], hypocalcemia, renal failure and hepatic failure [79].

3. Results

We reviewed 61 reports on TdP induced by antibiotics, 59 published reports [8–65,68] and 2 reports from pharmaceutical companies [80,81]. Overall, 78 patients with TdP induced by antibiotics were reported: 50 patients (64.1%) received macrolides, 25 (32%) received quinolones, 2 (2.5%) used trimethoprim–sulfamethoxazole and 1 used metronidazole (1.2%).

3.1. Prevalence of risk factors for torsades de pointes

The most commonly identified risk factor for TdP among patients with TdP induced by antibiotics was female gender (52/78, 66.7%). The vast majority of female patients were middle-aged or older women (44/52, 84.6%). The second most commonly identified risk factor for TdP among patients with TdP induced by antibiotics was advanced heart disease (46/78, 59%). Concomitant use of a QT interval-prolonging agent or an inhibitor of hepatic drug metabolism was present in 38/78 patients (48.7%); 10 patients took amiodarone and macrolides or quinolones or metronidazole; 9 took cisapride and macrolides or quinolones; 4 took disopyramide and macrolides; and 4 took terfenadine prior to macrolides. The remaining patients took antibiotics with digoxin (n = 3), astemizole (n = 2), quinidine (n = 2), fluconazole (n = 1), amitriptyline (n = 1), sotalol (n = 1) and pentamidine (n = 1). Hypokalemia was reported in 16/78 patients (20.5%). Eight patients (10.3%) had subclinical LQTS (Fig. 1).

3.2. Prevalence of risk factors for torsades de pointes by antibiotic classes

It was evident that, following female gender (33/50, 66%), the use of another QT interval-prolonging agent or an inhibitor of hepatic drug metabolism and the presence of advanced heart disease were the second and third most common risk factors for TdP among patients receiving macrolide antibiotics (54% and 50%, respectively). Advanced heart disease and female gender were the two most common risk factors for TdP among patients receiving quinolones (76% and 68%, respectively) (Table 1).
3.3. Number of risk factors for torsades de pointes

All but four patients with TdP induced by antibiotics (94.8%) had no less than one easily identified risk factor for TdP prior to initiation of antibiotic therapy. Moreover, 58/78 patients (74.3%) had two risk factors or more for TdP prior to initiation of antibiotic therapy. Overall, patients with TdP induced by antibiotics had 2.0 ± 0.9 risk factors for TdP prior to initiation of antibiotic therapy (Fig. 2).

It should be noted, however, that all four of the male patients with no risk factors for TdP prior to initiation of antibiotic therapy had clinical features associated with TdP: one elderly man who received intravenous erythromycin [21], one elderly man with renal failure and hypocalcemia [61], another elderly man with hepatic failure who received intravenous erythromycin [28] and, finally, an elderly man with renal failure [13].

3.4. Number of risk factors for torsades de pointes by gender

Although female gender was the most commonly identified risk factor for TdP among patients with TdP induced by antibiotics, 45 out of 52 female patients (86.5%) had additional risk factors for TdP and 6 out of 7 female patients without risk factors for TdP other than female gender had one or more clinical features associated with TdP. All six were elderly women, two of whom received intravenous erythromycin [20,26,31,47,55,58,63] (Fig. 2).

4. Discussion

The use of several antibiotics in the clinical setting may lead to prolongation of the QT interval and, on rare occasions, to TdP. The chance of provoking a fatal arrhythmia as the result of taking a “harmless” antibiotic agent is very troubling. Drug-induced TdP is considered unpredictable, although several risk factors for its occurrence have been established by unfortunate experiences [2]. In previous studies on patients with drug-induced TdP, it was apparent that risk factors for TdP had been prevalent prior to initiating therapy with the offending macrolides [78] and quinolones [52]. Contrary to these studies, this review included the most recent reports on TdP induced by antibiotics of all types. We found that all patients with TdP induced by antibiotics had at least one risk factor for TdP or a clinical feature associated with TdP that could have been easily identified prior to initiation of antibiotic therapy. For this reason, we wish to urge physicians to prescribe antibiotics only after careful clinical evaluation of risk factors for TdP.

4.1. Risk factors for torsades de pointes

The most commonly identified risk factors for TdP among all patients with TdP induced by antibiotics were female gender, advanced heart disease and concomitant use of a QT prolonging drug.
of a QT interval-prolonging agent or an inhibitor of hepatic drug metabolism. These observations are consistent with earlier reports. Women have an extended QT interval compared with men [82] and are at higher risk for TdP [69]. Heart failure downregulates potassium channels [83] and upregulates calcium channels [84], leading to action potential prolongation and higher risk for TdP [70]. Concomitant use of a QT interval-prolonging agent or an inhibitor of hepatic drug metabolism is a common risk factor for TdP among patients with macrolide-induced TdP [78], e.g., the concomitant use of cisapride and erythromycin, both CYP3A4 inhibitors [11]. It should be noted, however, that 46 out of 52 female patients (86.5%) had additional risk factors for TdP. Thus, the prevalence of risk factors for TdP among female patients was comparable to the prevalence of risk factors for TdP among male patients (84.6%). Moreover, six of the seven women without risk factors for TdP had clinical features associated with TdP.

4.2. Clinical implications

TdP due to non-cardiac drugs is a rare phenomenon [46]. The overwhelming majority of patients who developed this complication while being treated with antibiotics had had one or more easily identifiable risk factors to develop it in the first place or had clinical features associated with TdP. We believe that previous recommendations regarding taking measures before prescribing any drug that might induce TdP are also relevant in prescribing antibiotics that might induce TdP. Elderly women, individuals with advanced heart disease and patients who use more than one agent that might prolong the QT interval are at an increased risk for TdP and should be treated more cautiously. Obtaining a baseline electrocardiogram strip is also advisable [2].

4.3. Study limitations

Our study was based mostly on published case reports. We assume that there are many more incidents of TdP induced by antibiotics that have not been published, e.g., when a similar incident involving a given agent has already appeared in print several times, when a report is rejected for publication because TdP is attributed to early multiple risk factors for TdP rather than to initiating the offending drug, or when physicians are reluctant to report about the death of their patients. Cases of sudden death without documentation of an arrhythmia will also go unrecorded. We therefore believe that our results are more likely an underestimation of the true prevalence of risk factors for TdP among patients with TdP induced by antibiotics.

Only patients who actually developed TdP under antibiotic therapy were included in this study; patients under antibiotic therapy who did not develop TdP were excluded. Hence, we cannot estimate the likelihood of TdP occurrence among patients with risk factors for TdP who use antibiotics. We can only advise physicians to take into account this potentially lethal complication when prescribing antibiotics, i.e., macrolides, quinolones, trimethoprim–sulfamethoxazole and metronidazole, to patients at risk.

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