FOLLOW-UP SURVEY OF SIDE EFFECTS OF SINGLE DOSE CIPROFLOXACIN FOR PROPHYLAXIS OF MENINGOCOCCAL DISEASE IN A LOS ANGELES COUNTY HIGH SCHOOL

BACKGROUND

On November 14, 2006, two cases of invasive meningococcal disease (MD) occurring in students attending the same high school (HS) were reported to the Los Angeles County (LAC) Department of Public Health Department (DPH). One case was culture-confirmed with *Neisseria meningitidis* serogroup B bacteremia and the other was later PCR-confirmed with serogroup B meningococcal meningitis (culture-negative). The two students did not know each other and did not share common classes, friends or school activities. Following the confirmation of these cases, the LAC DPH stood up two point-of-distribution (POD) clinics to dispense prophylaxis for students and teaching staff at the HS who may have had contact with these students. The first clinic was held on the evening of November 14th, and an additional clinic the morning of November 15th. Parents and students were notified about the clinics through the school's automated phone message system, internet page, and a letter to parents. School officials released the names of the two ill students during the first clinic after obtaining parental consent, in an effort to identify the direct contacts that would require prophylaxis. Despite this, over 3000 persons were evaluated and 2861 persons were provided with single-dose ciprofloxacin prophylaxis.

As part of the routine public health follow-up of individual suspected and confirmed cases of invasive meningococcal disease, all contacts are evaluated for prophylaxis and educated on the symptoms of invasive MD. Mass prophylaxis is usually not considered except in situations which meet the Centers for Disease Control and Prevention (CDC) criteria for meningococcal outbreaks, defined as three or more cases within a three month period occurring in an institutional setting such as a school or among military [1]. The decision to provide prophylaxis on a mass basis rather than only to known close contacts of the case must be weighed against the risk of high numbers of reports of serious side effects associated with the prophylactic antibiotic, including anaphylaxis, to local health facilities, as well as the possibility of antimicrobial resistance developing within a contained community. In this situation, the decision was made to provide prophylaxis to self-identified close contacts through a distribution clinic because neither student could be interviewed to identify close contacts in a timely manner; and the extent of *N. meningitidis* carriage in this population could not be ascertained. Further, ciprofloxacin is generally well tolerated, having been utilized successfully without adverse events in other HS settings in California where mass prophylaxis had been required [California CD Brief, March 4, 2001]. Moreover, *N. meningitidis* has been rarely observed to be resistant to ciprofloxacin.

The use of ciprofloxacin in the pediatric and adolescent population has been limited because irreversible joint damage has occurred as a side effect in juvenile animal studies. Despite this, ciprofloxacin has been commonly used for children and adolescents when other treatment is not an option. Irreversible joint damage has never been found to occur [3-6]. District public health personnel documented only two major adverse events immediately following the clinic—two (0.07%) students developed rash without anaphylaxis. However, a number of adverse events may have gone unreported.

Two weeks after the POD clinics were held, LAC DPH conducted a follow-up survey study of all students and teaching staff of the high school in order to quantify possible side effects related to single-dose ciprofloxacin in an adolescent population and to evaluate the reasons such a large number of students and staff chose to receive prophylaxis despite being at low risk. Such a study would detect any minor or unreported adverse events that were not documented during the clinic or by another healthcare provider. Further, the results of the study may help provide information for future public health responses to both institutional outbreaks of infectious disease as well as bioterrorism events.

METHODS

As part of school policy, parents were notified prior to student participation in a follow-up POD clinic survey. Parents, students, and teaching staff were notified of the upcoming survey one week in advance via an automated phone message system and an announcement on the school's webpage. The survey was distributed to all HS teaching staff and students during their homeroom period on November 28, 2006. Completed surveys were collected by HS staff through December 3, 2006. Survey data included: demographics, the date of POD clinic attendance, reasons for attendance, side effects of single dose 500 mg ciprofloxacin, type of contact with the case students, health status at the time of the clinics, perception of risk of a variety of health conditions, and knowledge of MD. Respondents were asked to rate the importance of reasons for clinic attendance on a scale from 1 to 5, 1 being not important and 5 being very important. They were asked to rate their perception of risk of various health conditions on a similar scale as previously noted. The health conditions included meningitis and ranged from rare conditions such as avian influenza (referred to as "bird flu" on the survey) and cancer to more common conditions such as being in a traffic accident. Part of their knowledge of MD was assessed by asking students to identify the correct modes of transmission of MD. Data were entered into Microsoft Access and analyzed with SAS 9.1. Because of the known differences in the side effects and attitudes between adults and adolescents, the student and staff were analyzed as two separate populations. The differences in proportions were evaluated by chi square analysis and Fisher's exact test.

RESULTS

Surveys were distributed to 2888 students in attendance the day of the survey and 105 teaching staff in 105 homeroom classes. A total of 1717 completed surveys were returned (n=1649, or 57%, of students and n=68, or 65%, of teaching staff). All parents allowed the participation of their child on the survey. Twenty-seven surveys were excluded (2%) from the analysis because they did not contain enough information due to missing or inappropriate answers. A majority of the returned surveys (n=1690, 98%) from students and staff were available for analysis. Of these, 1624 (96%) were completed by students and 66 (4%) were completed by staff. Only results from the analysis of student surveys will be presented in this report.

Among all students who completed the survey, 49% were male and 50% were female. Students were distributed evenly among ninth to eleventh grades (26% to 28%), but there were slightly fewer 12th graders (18%). This is significantly different from the distribution of students at the high school ($p<0.0001$). The race/ethnicity distribution was 49% white, 33% Asian, 8% Latino, 6% were mixed race or other, and 2% were black. The distribution of whites, Asians, and Latinos is also significantly different from that of the high school ($p<0.0001$). Most of the students who completed the survey (n=1445, 89%) attended the clinics. More females than males attended the clinics (91% versus 87%, $p=0.0038$) All racial/ethnic groups attended the clinics at similar proportions (85% to 91%), with the exception of blacks, with only 74% reporting clinic attendance ($p=0.0231$) (Table 1).

The mean ratings of reasons for attendance among students ranged from 2.13 for having "contact with one of the sick students" to 3.97 for "parents told me to". Only 24% of student respondents rated the importance of having contact with the ill students as a 4 or 5. "Heard about it in the media" was rated second to last at 2.56 with only 30% of students rating its importance at 4 or 5 (Table 2).

Table 1. Differences in Characteristics of Students Completing Survey and Attending POD Clinics

			Surveyed Students				
		All HS Students n (%) (n=2962)	Total n (%) (n=1624)	p-value	Attend POD Clinics n (%)* of Surveyed Students (n=1445)	Did Not Attend POD Clinics n (%)* of Surveyed Students (n=179)	p-value
Gender	Male	1469 (50)	795 (49)	0.8578	689 (87)	106 (13)	0.0038
	Female	1493 (50)	817 (50)		745 (91)	72 (9)	
	Unknown	--	12 (1)	--	11 (92)	1 (8)	--
Grade	9th	782 (26)	419 (26)	<0.0001	366 (87)	53 (13)	0.1922
	10th	735 (25)	440 (27)		385 (88)	55 (12)	
	11th	742 (25)	459 (28)		416 (91)	43 (9)	
	12th	703 (24)	292 (18)		266 (91)	26 (9)	
	Unknown	--	14 (1)	--	12 (86)	2 (14)	--
Race	Asian**	829 (28)	530 (33)	<0.0001§	480 (91)	50 (9)	0.0231
	Black***	--	27 (2)		20 (74)	7 (26)	
	Latino	237 (8)	135 (8)		117 (87)	18 (13)	
	White	1807 (61)	799 (49)		714 (89)	85 (11)	
	Mixed/Other***	89 (3)	104 (6)		88 (85)	16 (15)	
	Unknown	--	29 (2)	--	26 (90)	3 (10)	--

* Percentages tabulated across rows, not columns.
** Includes Filipinos in surveyed students but excludes Filipinos among all HS students.
*** Includes mixed race and American in surveyed students but excludes Black, American Indian, Filipino, and Pacific Islander among all HS students.
§ Chi square test performed only among Asian, Latino, and White race categories.

Of the 1445 students who attended the clinics, 1390 (96%) took the ciprofloxacin. Table 3 lists the main side effects experienced by 608 students (44%) after taking the antibiotic. Most (69%) were able to recall an onset time. Among these, 57% reporting experiencing side effects from one to six hours after ingesting the single dose of ciprofloxacin. The median onset time was three hours. A greater proportion of females reported side effects compared to males (49% versus 39%), (p=0.0002). The most common side effects reported were headache (20%) and stomachache (12%), followed by sore throat, restlessness and muscle pain (each at 6%). Other notable side effects occurring less commonly were nausea/vomiting (5%), itching (3%), rash (2%), difficulty breathing (2%), and one case of face swelling. No joint pain was reported.

Table 2. Reasons for Clinic Attendance among Students

Reason for Attendance	Mean Rating of Importance	% Rated 4 or 5
Parents told me to	3.97	71
Heard phone message/ Received letter from school	3.34	51
Fear of serious illness or death	3.24	48
Friends did it	2.87	36
Advised by physician	2.63	35
Heard about it in the media	2.56	30
Had contact with one of the sick students	2.13	24

There was a significant difference in the proportion that reported side effects in those already ill compared to those who were not ill (60% versus 40%, p>0.0001). The most common side effects among those who were not already ill at the time of the clinics included: headache (17%), stomachache (10%), followed by restlessness, muscle pain, sore throat and nausea/vomiting (each at 4%) (Table 3).

Table 3. Reported Side Effects among Students Who Took Single Dose Ciprofloxacin (500mg)*

	All n (%) (n=1390)	No Illness Report at Time of POD Clinics n (%) (n=1153)	Illness at Time of POD Clinics n (%) (n=237)
≥1 Side Effect	608 (44)	465 (40)	143 (60)
Fever	48 (3)	28 (2)	22 (9)
Cough	72 (5)	33 (3)	39 (16)
Sore Throat	83 (6)	44 (4)	39 (16)
Headache	281 (20)	191 (17)	90 (38)
Watery Eyes	40 (3)	26 (2)	14 (6)
Stomachache	166 (12)	116 (10)	50 (21)
Itching	40 (3)	27 (2)	13 (5)
Rash	21 (2)	10 (<1)	11 (5)
Diarrhea	33 (2)	21 (2)	12 (5)
Nausea/ Vomiting	67 (5)	42 (4)	25 (11)
Difficulty Breathing	22 (2)	11 (<1)	11 (5)
Muscle Pain	79 (6)	45 (4)	34 (14)
Anxiety	24 (2)	12 (<1)	12 (5)
Restlessness	80 (6)	51 (4)	29 (12)
Tired	32 (2)	29 (3)	0 (0)
Muscle Stiffness	5 (<1)	4 (<1)	1 (<1)
Face swelling	1 (<1)	1 (<1)	0 (0)

*Students can have more than one side effect

A considerable number of students completing the survey (n=282, 17%) reported experiencing symptoms from other illnesses at the time the POD clinics were set up (Table 3). This is the same prevalence of illness among students who attended the clinic and took the antibiotic. There was no significant difference in the prevalence of illness between students who attended and did not attend the POD clinics. Among those who took the antibiotic, coughing was mentioned most frequently (n=110, 8%) as a symptom experienced at the time of the clinic. Fifty-one (4%) mentioned a headache and 70 (5%) mentioned a stomachache (Table 4).

Table 4. Reported Symptoms from Illness Experienced by All Students at the Time of the POD Clinics*			
Symptoms	**All Students n (%) (n=1624)**	**Took Ciprofloxacin n (%) (n=1390)**	**Did Not Take Ciprofloxacin n (%) (n=282)**
Total Ill	282 (17)	237 (17)	45 (16)
Fever	82 (5)	68 (5)	14 (6)
Cough	138 (9)	110 (8)	28 (12)
Headache	58 (4)	51 (4)	7 (3)
Stomachache	81 (5)	70 (5)	11 (5)
Sneezing	65 (4)	54 (4)	11 (5)

*Students can have more than one side effect

The majority of all student respondents (n=1223, 75%) had no contact with either of the cases. Only 50 (3%) reported sharing an item such as a cigarette, food or drink—activities that would put these students at highest risk for MD. The most frequent type of contact reported was being in the same class with the cases (n=158, 10%). Other types of contact listed included indirect relationships to the cases (e.g., friends of siblings) (n=67, 4%) and having casual direct contact with the cases (n=43, 3%).

Table 5 lists adverse health conditions, including meningitis, in decreasing order of mean rating of perceived risk. The students rated their risk of meningitis very low (mean of 1.49) relative to the other listed health conditions. Very few (5%) rated their risk as a 4 or 5.

Table 5. Perceived Risk of Various Health Conditions		
Health Condition	**Mean Rating of Perceived Risk**	**% Rated 4 or 5**
Common cold	3.41	49
Other injury	2.86	31
Flu	2.68	27
Traffic accident	2.54	21
Food poisoning	2.14	12
Cancer	1.77	9
Obesity-related disease	1.73	10
Meningitis	1.49	5
Bird flu	1.35	3

Sixty-nine percent (n=1113) of student respondents reported not having knowledge of MD prior to the incident. These students attended the clinic in a larger proportion than those who reported having some knowledge of MD (90% versus 87%, p=0.032). Students who incorrectly identified touching objects touched by case students as a transmission mode attended the POD clinic more often (92% versus 86%, p =0.0007).

DISCUSSION

The POD clinics provided public health officials with a rare opportunity to detect side effects of single dose ciprofloxacin in a healthy adolescent population. The follow-up survey conducted two weeks after the clinics were held enabled documentation of a 44% overall rate of side effects, or a rate of 40% among students who were not already ill at the time of the clinic. These included both minor side effects as well as more serious ones that may have been related to anaphylaxis. The survey results also helped public

health to deduce the main reasons for participation in a prophylaxis clinic involving a single dose of an oral antibiotic in a high school setting.

The overall frequency of side effects from ciprofloxacin reported in this adolescent population (44%) is similar to that reported for this age group in the Physicians Desk Reference (PDR), which reported a rate of 41% from a clinical trial among complicated urinary tract infection patients prescribed ciprofloxacin [2]. The frequencies of individual symptoms in this population differ substantially than what is listed in the PDR and other pediatric studies. The most commonly reported side effects associated with ciprofloxacin among children and adolescents are gastrointestinal (including nausea, diarrhea, vomiting, and abdominal pain), central nervous system (headache and restlessness), and dermatologic symptoms. This study reports headache in 17% of healthy students, stomachache in 10%, and no joint-related disorders. In the PDR, gastrointestinal symptoms occurred in 15% of patients, musculoskeletal symptoms in 9.3%, abdominal pain in 3.3%, and headache in less than 1% [2]. A few other pediatric studies have shown similar rates of gastrointestinal symptoms that have ranged up to 14.5%. Neurological symptoms, which may include headache, in these same studies, however, range only up to 4.8% [5]. Most other studies report much lower rates of specific symptoms: abdominal pain ranged from 1% to 5% and headaches from 0% to 4% [4-6]. The frequency of joint disorders in these studies, however, are higher than this findings and ranged from 1% to 22% [3-6].

Prior to the implementation of the survey, only two adverse events were documented—two students with rash who required oral Benadryl®. The survey revealed multiple other occurrences of rash and itching (2% and 3%, respectively) as well as breathing difficulties (2%) and a case of facial swelling—all possible anaphylactic reactions to ciprofloxacin which were not reported to public health prior to the survey. The frequency of these symptoms falls within range of other referenced pediatric studies. Itching and rash, for example, are seen in about 2% of patients in these published studies. Vomiting occurred in 2% to 5% of patients [2,4,6].

The high rates of adverse events seen in this study compared to previously published pediatric studies can be explained by the use of ill or hospitalized populations in these studies. In this patient setting, study participants are most likely in a controlled environment where interactions with substances commonly consumed by adolescents such as caffeine and nicotine are limited or nonexistent. Ciprofloxacin can act to increase the effects of caffeine in particular, and this most commonly reported symptoms are also known side effects of caffeine, including headache, stomachache or abdominal pain, and restlessness and anxiety [2]. In addition, the lack of serious illness in this study population may have promoted detailed recall of minor symptoms that may be overlooked or unimportant in an ill population. It has been documented that even among healthy persons who were not taking any medications, minor symptoms such as headache, fatigue, and drowsiness, are common [7]. Benign bodily symptoms such as these may be mistakenly attributed to side effects of medication. This phenomenon would be emphasized as the high school population was in the midst of the fall/winter “cold and flu season” and already experiencing a general illness rate of 17% at the time of the clinic.

Conversely, there is a superior ability to detect side effects in patient populations because of the availability of healthcare professionals and special monitoring. Further, the follow-up time in these patient population studies ranged from 20 days to 6 weeks, longer than the two week follow-up period of this study, enabling a greater window of time to detect side effects. These populations also underwent longer treatment courses and higher doses of ciprofloxacin whereas this student population took only one single dose.

Few associations were found to be significant that could explain the high rates of attendance and subsequent acceptance of antibiotic prophylaxis. A minority of surveyed students (25%) had any contact with the students, and much fewer (3%) had direct contact that may put them at risk for MD. Accordingly, having contact with the case students did not factor heavily in their decision to attend the clinic. Interestingly, experiencing current symptoms of illness was not a factor in either attendance or intake of antibiotic. Having better knowledge of meningitis and the methods of transmission was some indicator of attendance and antibiotic intake. Though the students understood that they were at low risk of meningitis, rating it nearly last only before avian influenza, a large majority of the student population attended the

clinic. Because “fear of serious illness or death” was rated relatively high, it appears that students and staff felt that even at low risk, the consequence was serious enough to warrant prophylaxis.

Evidence suggests that school and public health officials may have inadvertently encouraged all students and staff to seek prophylaxis. Hearing the school’s telephone message or receiving the letter from the school administrators was rated among the highest as an important reason for attending the clinics. It has been suggested that parents and students were highly influenced by the advice of their personal physicians or the message given by the media, namely, that there was a “meningitis outbreak”, despite the fact that public health officials made it clear that one confirmed case and a suspected case did not meet the definition of an outbreak. However, “advised by a physician”, as well as “heard about it in the media” even more so, had lower mean ratings of importance. Furthermore, the health announcement the HS administration initially composed did not specifically focus enough on close contacts and may have also communicated heightened fear and risk. Though the names of the case students were released in order to limit attendance, they were announced to parents and students as the first clinic was already underway. Finally, the structure of the POD clinic itself did not alleviate the high attendance as it was designed more for distributing medication rather than assessing risk and need.

A major limitation of the study was the lack of a placebo group to determine if symptoms reported were a side effect of ciprofloxacin alone. This would not have been feasible or appropriate in a public health response setting without prior approval from an Institutional Review Board. In such a study, factors such as interactions with additional consumed substances or the background prevalence of illness would be controlled for. The survey was implemented two weeks after the clinic event, increasing recall bias of reported symptoms, particularly as most symptoms had an onset within six hours after ingestion of the antibiotic. The lag time in survey implementation may also have influenced the response rate of the survey: only 57% of students in attendance that day completed the survey. The surveyed students were not representative of the school as there were differences in rates of participation among grade levels and race/ethnicity groups. Lastly, the survey was self-administered without the presence of public health staff, which could have decreased the validity of many answers, especially the self-report of symptoms.

Despite these limitations, the results of this study fell within range of adverse events found in previous studies. As adverse events from ciprofloxacin in pediatric populations have often been studied in patient groups, this study added insight on how ciprofloxacin may affect a healthy population. Though the occurrence of side effects approached the higher range of published rates, the side effects were minor and most did not require medical attention. The lack of any joint-related side effects also further supports the safety of ciprofloxacin in the pediatric population as seen in previous studies, especially in the setting of single dose usage. These results provide a realistic assessment of the frequency and severity of side effects that would be useful for other situations of mass prophylaxis, for both common outbreaks as well as bioterrorism events.

Additionally, the results of this study indicate that parents and students are reasonable and rational in the face of the threat of a serious disease and are highly influenced by the advice of school officials. Public health officials must work closely with schools to explain the risk of disease and advise on appropriate prophylaxis distribution. Presenting a balanced message by communicating the risks of unnecessary use may encourage more prudent use of the antibiotic prophylaxis.

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