THE PREVALENCE OF SIDE-EFFECTS: CIPROFLOXACIN 500 MG SINGLE DOSE PROPHYLAXIS AGAINST *NEISSERIA MENINGITIDIS* OUTBREAK IN POTCHEFSTROOM DURING JULY 2003

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ABSTRACT

Potchefstroom experienced an outbreak of Neisseria meningitidis (N. meningitidis) during May-July 2003. An opportunity for obtaining valuable data arose when mass prophylactic treatment to approximately 28% of the Potchefstroom community was provided by the Department of Health, North-West Province. The aim of this study was to investigate the prevalence of side-effects experienced by staff and students of the Potchefstroom University for Christian Higher Education (PU for CHE) who received a single prophylactic dose of oral ciprofloxacin 500 mg between 23 and 29 July 2003. Information gained from the Potchefstroom outbreak may be valuable for the future management of similar outbreaks in other communities. Various stakeholders have published related reports, protocols, recommendations and guidelines, which mostly focused on the prevention, management and control of meningococcal disease. Very little has been reported about the side-effects experienced, especially in cases where ciprofloxacin 500 mg single dose had been dispensed. One or more side-effects were reported by 24.2% of the participants, while 5.4% had to consult with a health care worker due to the severity of side-effects resulting from a single dose. Practical significance could not be demonstrated for any of the side-effects reported after single versus multiple doses nor when the effects of gender or requirement for medical consultation were tested.

OPSOMMING

'n Uitbraak van Neisseria meningitidis (N. meningitidis) gedurende Mei-Julie 2003 en die daaropvolgende verskaffing van massa-profilakse deur die Departement van Gesondheid, Noordwesprovinsie aan ongeveer 28% van die plaaslike gemeenskap het 'n geleentheid geskep om waardevolle inligting in te win. Die doel van die studie was om die voorkoms van newe-effekte te ondersoek wat deur die personeel en studente van die Potchefstroomse Universiteit vir Christelike Hoër Onderwys ervaar is na toediening van 'n enkel profilaktiese dosis van siprofloksasien 500 mg tussen 23-29 Julie 2003. Inligting wat hieruit voortspruit mag waardevol wees tydens toekomstige bestuur van uitbrake in ander gemeenskappe. Verskillende belanghebbendes het verslae, protokolle, aanbevelings en riglyne gepubliseer, wat meestal op die voorkoming, bestuur en beheer van meningokokkale siekte gefokus het. Daar is egter min gerapporteer oor die newe-effekte wat ondervind is veral waar siprofloksasien 500mg enkeldosis toegedien is. Een of meer newe-effekte is deur 24.2% van die deelnemers ervaar en 5.4% het dit nodig geag om 'n gesondheidswerker te konsulteer in verband met die newe-effekte wat ervaar is. Geen prakties betekenisvolle

verskille is aangedui indien die effeksgrootte bereken is vir die newe-effekte getoets tussen die enkeldosis versus die meervoudige dosis nie, selfs ook nie nadat die effek van geslag of konsultasie getoets is nie.

INTRODUCTION

"*Few infections can cause the civil, medical, and social stress that occurs when serious meningococcal disease enters a community*" (Apicella, 1995:2).

Meningitis is an inflammation of the meninges (the membranes surrounding the brain and spinal cord). Meningitis can be caused by either bacterial or viral infection. Various bacteria can induce meningitis but the most common causes of the reported cases were *N. meningitidis* (meningococcus) and *Streptococcus pneumoniae* (pneumococcus) (Beers & Burkow, 2003:1). Until recently, *Haemophilus influenzae* type b was the most common cause of meningitis in children older than one month, but vaccination dramatically reduced the incidence (Beers & Burkow, 2003:1). Meningococcus is a serious life-threatening condition that requires immediate medical treatment.

N. meningitidis causes both sporadic disease and outbreaks all over the world. Various reports, protocols, control measures, guidelines, recommendations and policy strategies have been drafted and implemented in order to control and manage the disease (American Academy of Pediatrics, 2000:1500; Centers for Disease Control and Prevention (CDC), 2000:11; Canada Communicable Disease Report, 1994:1825). These mostly deal with the prevention, management and control of meningococcal disease. Very little was reported in these publications about the medication side-effects, especially in cases where a single dose of ciprofloxacin 500 mg was dispensed.

Since 1991, the frequency of localised outbreaks of *N. meningitidis* in the United States of America (USA) increased, especially among college students and recruits in the military. Students, recruits and other military staff living in crowded conditions experience an increased risk for meningococcal infection. For this reason, a vaccine that is protective against four types (A, C, W-135, Y) of *N. meningitidis* is given to basic trainees and college freshmen, particularly those who live in dormitories (CDC, 2000:11).

STUDY PURPOSE AND RATIONALE

The purpose of this study was to investigate the prevalence of side-effects experienced by staff and students of the Potchefstroom University for Christian Higher Education (PU for CHE), now the Potchefstroom campus of the North-West University) who received a single prophylactic dose of oral ciprofloxacin 500 mg between 23 and 29 July 2003. The efficacy of ciprofloxacin chemoprophylaxis is not disputed or questioned, the side-effects are well reported in various recognised pharmacological literature. However, very little was reported about the side-effects experienced in cases where ciprofloxacin 500 mg single dose was administered.

Eight confirmed cases of meningitis were reported in the greater Potchefstroom district from May – 30 July (Joint Task Team: Provincial and Local Health Authorities and PU for CHE, 2003c). Five confirmed cases were of students from different tertiary institutions in the city. Three students died and two were treated and discharged from hospital (Joint Task Team: Provincial and Local Health Authorities and PU for CHE, 2003a). Two of the deceased students were from the PU for CHE and they passed away on 23 July (PU for CHE, 2003) and 27 July 2003 respectively (Joint Task Team: Provincial and Local Health Authorities, World Health Organisation (WHO) and the Potchefstroom University, 2003b).

A joint task team headed by doctor TGK Oosthuizen (Chief Director Health Service Delivery, Department of Health, North-West Province) was formed by 28 July 2004 and a decision was made to dispense mass ciprofloxacin 500 mg tablets on 28 July 2003 between 16:00 and 22:00 to staff and students of all the tertiary institutions in the city (Joint Task Team: Provincial and Local Health Authorities and the PU for CHE, 2003c). The rationale was to attempt a simultaneous mass eradication of the *N. meningitidis* bacteria in the population of possible carriers of these bacteria.

An opportunity arose to gather data concerning the prevalence of side-effects after a single prophylactic dose of oral ciprofloxacin 500 mg was administered on such a large scale and the focus of this investigation was only on the staff and students of the PU for CHE (Potchefstroom campus) in the time period 23-29 July 2003.

PROPHYLACTIC TREATMENT OF MENINGITIS

Chemoprophylaxis is highly effective in some clinical settings and in others it is totally without value and may be deleterious. The use of antimicrobial compounds to prevent infections remains controversial in several situations (Chambers, 2001:1164). The purpose of chemoprophylaxis is to eradicate nasopharyngeal colonisation by *N. meningitidis*, which prevents the disease in contacts and its transmission to non-immune susceptible people. Chemoprophylaxis is not effective in preventing a disease once invasion of tissue has taken place (Canada Communicable Disease Report, 1994:1826).

A comprehensive report was published by the Canadian Paediatric Society (CPS), Infectious Diseases and Immunization Committee, American Academy of Pediatrics (AAP) and the Committee on Infectious Diseases in 1997, which was reaffirmed in February 2003, in which they addressed meningococcal disease prevention and control strategies for practice-based physicians. In their joint statement they stressed that chemoprophylaxis is indicated for close contacts of all persons with invasive meningococcal disease, whether sporadic, or in a cluster or outbreak. The CPS and the AAP currently recommend antimicrobial chemoprophylaxis for contacts of persons with invasive meningococcal disease, including household members, individuals in childcare centres and nursery schools, and persons directly exposed to oropharyngeal secretions through kissing or sharing of food or beverages during the seven days before the onset of disease in the index case. Prophylaxis is not recommended routinely for medical personnel except for those who have had intimate exposure, such as that which occur with mouth-to-mouth resuscitation, intubation or suctioning. The index case should also receive chemoprophylactic antibiotics before discharge unless treated with ceftriaxone. Because the attack rate of secondary disease after a close contact is highest in the few days following the onset of disease in the primary case, the delay in providing antimicrobial chemoprophylaxis must be minimised and, ideally, the prophylaxis should be given within 24 hours of case identification. Suggested chemoprophylaxis regimens include rifampin (rifampicin), ceftriaxone and ciprofloxacin and these are shown in Table 1.

Various health departments (Welsh Medicines Information Centre, 2003:5; Massachusetts Department of Public Health, 1999:7) follow similar guidelines as reflected in Table 1 for chemoprophylaxis but for pregnant women they also include Ceftriaxone 250 mg as a single dose, administered intramuscularly.

The WHO provided chemoprophylactic guidelines similar to those reflected in Table 1, but also included spiramycin or minocycline for five days as alternatives (WHO, 1998:28). Their report did not recommend mass chemoprophylaxis to prevent or control epidemics.

Oral rifampicin had been the drug of choice for chemoprophylaxis in recent decades. Rifampicin is 72% to 90% effective in eradicating nasopharyngeal carriage and serious adverse effects with short-term therapy are rare. Urine and stools may be stained orange or red and soft contact lenses may become tinted and therefore warnings would be required. Rifampicin may also interfere with the efficacy of oral contraceptives and is not recommended for use during pregnancy. The impact of rifampicin on the metabolism of other medications such as those for seizure prevention and anticoagulation must also be considered. Ceftriaxone administered as a single intramuscular dose is an alternative to rifampicin and is more than 95% effective in eradicating carriage. In adults who are not pregnant, a single dose of ciprofloxacin is an effective oral alternative to rifampicin in 90% to 95% of cases. Although ciprofloxacin is used in children for chemoprophylaxis of meningitis, it is not currently approved for use in children younger than 18 years and should not be used when safer alternatives are available (CPS, 1997:5; Petri, 2001:1182). Although sulphonamides were effective in preventing disease for many years, the majority of isolates of *N. meningitidis* of serogroups B and C in the USA as well as group A isolates from other countries are now resistant (Petri, 2001:1172).

CIPROFLOXACIN

Table 1: Recommended chemoprophylaxis regimens for high-risk contacts and index cases of invasive meningococcal disease

Infants, Children Adults	Dose	Duration	Efficacy (%)	Cautions
Rifampicin*				
<1 month	5 mg/kg oral every 12h	2 days	72 90	May interfere with efficacy of oral contraceptives, some seizure prevention and anticoagulant medications
>1 month	10 mg/kg (maximum 600 mg) oral every 12h, 20 mg/kg (maximum 600 mg) oral every 24h	2 days 4 days		May stain soft contact lenses
Ceftriaxone				
< 12 years	125 mg I.M.	Single dose	97	To decrease pain at injection site, dilute with 1% lidocaine
>12 years	250 mg I.M.	Single dose		
Ciprofloxacin*				
18 years	500 mg oral	Single dose	90 95	Not recommended for use by children

* Not for use by pregnant women.

Information in Table 1, taken from a joint report of the Canadian Paediatric Society (CPS), Infectious Disease and Immunization Committee, American Academy of Pediatrics (AAP) and the Committee on Infectious Diseases, 1997.

Single dose ciprofloxacin was shown to be effective in eradicating pharyngeal carriage of *N. meningitidis* by Gaunt and Lambert (1988:489) when 2100 navy personnel received single oral doses of ciprofloxacin 500 mg and 570 of the personnel were swabbed 2-4 days later. An additional 277 personnel members were followed-up for nine weeks afterwards to determine the elimination rate of the pharyngeal carriage. The overall prevalence of carriage declined from 19% to less than 1.5% as a result of the use of ciprofloxacin.

Ciprofloxacin is one of a number of fluorinated 4-quinolones and is of great importance therapeutically due to the agent's broad antimicrobial activity. It is effective after oral administration for the treatment of a wide variety of infectious diseases (Petri, 2001:1182).

Side effects of ciprofloxacin

Fluoroquinolones are generally well-tolerated. The most common adverse reactions involve the gastrointestinal tract (nausea, vomiting and/or abdominal discomfort reported by 3% to 17% of the patients). Central nervous system side-effects, predominantly mild headache and dizziness have been reported in 0.9% to 11% of patients. Skin rashes, including photosensitivity reactions (sensitivity of the skin to direct sunlight), may occur. Allergic reactions have been described, such as hives (urticaria) and anaphylaxis (Petri, 2001:1182).

Three cases of anaphylactic reactions (a rate of about 1:1000, much higher than the 1:100 000 quoted) were reported in approximately 3200 first-year university stu-

dents who accepted single dose ciprofloxacin 500 mg as prophylactic treatment (Burke & Burne, 2000:679).

Side-effects reported by naval training personnel after receiving a single dose of oral ciprofloxacin 500 mg were mild in nature with the exception of one recipient who developed an acute urticarial reaction ten minutes after taking the tablet (Gaunt & Lambert, 1988:493).

Quinolones and fluoroquinolones cause arthralgias (pain in joints) and joint swelling in children receiving ciprofloxacin and are, for that reason, not recommended for use in pre-pubertal children or pregnant women. Leucopoenia, eosinophilia and mild elevations in serum transaminase rarely occur (Petri, 2001:1182).

Many antibiotics, including ciprofloxacin, can alter the normal bacteria in the colon and encourage overgrowth of bacteria responsible for the development of inflammation of the colon (pseudomembranous colitis), causing fever, abdominal pain, diarrhoea, and sometimes even shock (Petri, 2001:1182).

STUDY METHOD

Research Design and Setting

An open non-randomised study was conducted, based on a *voluntary and anonymous* questionnaire distributed in Afrikaans, English and Setswana (refer to addendum) on 31 July 2003 (three days after mass prophylaxis) to students and staff of the PU for CHE. It was decided to target the maximum possible number of participants by posting the questionnaire electronically on the bulletin board of the PU for CHE. In addition, 3500 printed copies were distributed as follows:

a) to the respective House Committee representatives of all residences on and off campus;
b) to two libraries (left at the entrances of the libraries) on campus; and
c) to various departments to include all the workers employed in the kitchens, gardens and hostels together with possible subcontractor workers at that time.

The questionnaire had to be returned on or before 6 August, 2003.

Study Population

A total of 9 075 single prophylactic doses of ciprofloxacin 500 mg tablets were dispensed to staff and students of the PU for CHE as follows:

a) prior to 28 July 2003 (direct contacts to positively diagnosed cases): 539 single doses;
b) mass issue on 28 July 2003: 8 525 single doses;
c) issue on 29 July 2003 (to staff and students not available on 28 July 2003): 11 single doses;
d) 9075 Single doses of ciprofloxacin 500 mg were issued;
e) 1 537 individuals (16.9%) voluntarily completed questionnaires and returned them to the Department of Pharmacology before or on the set due date (Joint Task Team: Provincial and Local Health Authorities and PU for CHE, 2003c).

Validity and Reliability

The following actions were taken in order to ensure the reliability and validity (face and content) of the questions in the questionnaire:

a) special attention was given to ensure that each question only implied one concept; and
b) different preliminary versions of the questionnaire were drawn up and evaluated by various experts in the field of pharmacology, pharmacy practise and statistics.

An application for approval of the study was submitted to the Ethics Committee of the PU for CHE and to the Department of Health, North-West Province and both approved the study.

Statistical Analysis

The SAS System for Windows (SAS Institute, 2001) was used to create the database and to analyse the data by calculating certain descriptive and inferential statistics. The descriptive statistics included frequency tables, histograms and percentage expressions. Chi-square tests (χ^2) were used as inferential statistics to determine whether a difference existed between the side-effects reported by the participants who received only a single dose versus the participants who received multiple dose ciprofloxacin 500 mg; single dose versus gender effect, multiple dose versus gender effect and single dose-gender versus consultation required.

Because the responses were voluntary, the participants were not randomly selected. As a result, the following equation and guidelines were used to interpret the practical significance (the effect size) of the results (Steyn, 2002:11):

$$w = \sqrt{\frac{\chi^2}{n}}$$

where (χ^2) is the usual Chi-square statistic for a two-way frequency table and n = number of participants. The guidelines used to interpret the results followed the criteria provided by Cohen (1988:227):

w = 0.1 small effect (non significant)
w = 0.3 (medium effect)
w = 0.5 large effect (significant and of practical importance)

RESULTS AND DISCUSSIONS

Table 2 indicates that 1537 questionnaires were received from voluntary participants. Table 2 reflects the general demographic details of the participants. Table 4 reflects that 51.4% (741) of the participant (N=1443.94 missing data) indicated that they took a single dose treatment and 48.6% (702) indicated that they took more than one dose of ciprofloxacin 500 mg during the time period 25 - 29 July 2003. The female participants represented 65.4% (N = 731, 10 missing data) and the male participants represented 34.6% of the voluntary single dose study population.

The data reflected in Table 3 indicate the frequencies and percentages of all the side-effects reported by the participants (expressed as a percentage of 741 participants) who indicated that they took a single dose of ciprofloxacin 500 mg. All the responses of the participants (staff; on-campus students; and off-campus students) were combined and the gender contributions are reflected.

The data in Figure 1 indicate the percentage of side-effects greater than 1%, as reported by the participants who indicated that they took a single dose of ciprofloxacin 500 mg (expressed as a percentage of 741 participants). These side-effects included headache (9.3%), nausea (8.5%), sleepiness (8.0%), dizziness (5.9%), stomach cramps (4.6%), listlessness (3.4%), trembling (2.2%), insomnia (1.8%), diarrhoea (1.4%), itchiness (1.2%) and heart palpitations (1.1%).

Table 4 comprises comparative data with respect to the number of participants who experienced side-effects due to single dose versus multiple doses and the number of participants who consulted a healthcare worker due to the side-effect(s) they experienced. It is indicated that 392 (25.5%) of the 1537 participants (295 females or 19.2% and 97 males or 6.3%) reported one or more side effects. Of these 392 participants, 179 participants (11.6%) indicated that they took a single dose and 189 (12.3%) participants indicated that they took more than one dose of ciprofloxacin (24 (1.6%) participants did not indicate their dosage).

Of the 1537 participants 78 (5.1%), 40 on a single dose and 36 on multiple doses, (two did not indicate their dosages) indicated that they had to consult a healthcare worker about the side-effects experienced as a result of taking ciprofloxacin.

The side-effects for which further medical consultation was required after single dose ciprofloxacin 500 mg are shown in Figure 2. These side-effects are also expressed as a percentage of 741 single dose participants, constituting headache (2.0%), nausea (1.9%), dizziness (1.8%), sleepiness (1.5%), stomach cramps (0.9%), listlessness (0.7%), diarrhoea (0.54%), trembling (0.54%), insomnia (0.4%), heart palpitations (0.4%), vomiting (0.3%), convulsions (0.3%), skin rash (0.3%), visual disturbances (0.1%), joint pains (0.1%), redness of skin (0.1%), itchiness (0.1%), tiredness (0.1%), cold and flu symptoms (0.1%), neck pain/stiffness (0.1%), hypertension (0.1%), sore throat (0.1%) and fever (0.1%). Headache, nausea, dizziness and sleepiness were thus the only side-effects reported with a prevalence of greater than 1% after administration of a single dose of ciprofloxacin 500mg for which further medical consultation was required.

The SAS-calculated Chi-square-values (χ^2) for all the various side-effects due to a single dose, and those due to multiple doses, were used in the effect size equation to establish whether the effects experienced were significant. None of the w-values reached significance. The effect of gender was tested on the different side-effects reported with a single dose as well as with the side-effects reported after ingestion of multiple doses. Once again, no significance due to gender differences could be shown for any of the side-effects. The effect size tested to measure the relationship be-

Table 2: Demographic details of all voluntary participants

	Staff	Off campus students	Hostel students (On campus)	Others	TOTAL
Female	104	204	710	4	1022[B]
Male	47	125	328	2	502[B]
TOTAL	**151**	**1380[B]**		**6**	**1537**
Average age in years (Std. Dev.)	42.13 (11.9)	19.96 (1.75)		34.17 (18.48)	
Pregnant					3
Breast feeding					2
Medication obtained from:					
PUK Campus	1270				
Potchefstroom Hospital	18				1288
Municipal clinics	5				1293
Retail pharmacies	141				1434
Other	77				**1511[C]**
Details of dose and frequency:					
Single dose prophylactic treatment	478 = Female	253 = Male	10 = no gender specified		741
Multiple prophylactic treatment	481 = Female	218 = Male	3 = no gender specified		702
TOTAL					**1443[D]**

A= The participants indicated as "others" are family members (children and spouses) of staff members who also completed the questionnaire by choice.

B= 13 participants indicated that they were students (off-campus and on-campus) but did not indicate their gender.

C= 26 participants did not indicate where they received their treatment.

D= 94 participants did not reply to this section by indicating whether or not they took a single or multiple dose.

tween the side-effects due to a single dose, gender or causing consultation requirement with a health care worker, also indicated no practical significance. These results are not included, as no significance could be shown.

The information obtained through this questionnaire on possible drug interactions and the effect thereof on greater side-effect prevalence was not included in the scope of this article but the data is available for further statistical analysis.

Limitation of the study

In order to obtain a reliable response in the shortest possible time following the outbreak and accompanying prophylactic treatment, the design and execution of the study were somewhat complicated by the high level of social fear surrounding the outbreak. As a result, the decision to conduct this investigation was only made after the mass prophylaxis exercise had been completed. Therefore, the opportunity to issue the questionnaire simultaneously with the medication was lost, which could have impacted negatively on the response rate. However, in support of the method used the possibility of perceived side-effects being reported was eliminated.

CONCLUSIONS

One of the main aims of this study was to investigate the prevalence of side-effects after the administration of a single dose of ciprofloxacin 500 mg. It is apparent from the data analysis of the 1537 voluntary partici-

Table 3: Frequencies and percentages of all the side-effects reported (SINGLE DOSE)

	FREQUENCY			PERCENTAGE %		
SIDE-EFFECT	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
Headache	52	17	**69**	7.02	2.29	**9.3**
Nausea	48	15	**63**	6.48	2.02	**8.5**
Sleepiness	47	12	**59**	6.34	1.62	**8.0**
Dizziness	36	8	**44**	4.86	1.08	**5.9**
Stomach cramps	21	13	**34**	2.83	1.75	**4.6**
Listlessness	17	8	**25**	2.29	1.08	**3.4**
Trembling	14	2	**16**	1.89	0.27	**2.2**
Insomnia	9	4	**13**	1.21	0.54	**1.8**
Diarrhoea	5	5	**10**	0.67	0.67	**1.4**
Itchiness	7	2	**9**	0.94	0.27	**1.2**
Heart palpitations	6	2	**8**	0.81	0.27	**1.1**
Vomiting	5	2	**7**	0.67	0.27	**0.9**
Skin rash	5	1	**6**	0.67	0.13	**0.8**
Visual disturbances	4	1	**5**	0.54	0.13	**0.7**
Redness of skin	5	0	**5**	0.67	0.00	**0.7**
Joint pains	3	1	**4**	0.40	0.13	**0.5**
Tiredness	2	2	**4**	0.27	0.27	**0.5**
Thirst	2	1	**3**	0.27	0.13	**0.4**
Convulsions	1	1	**2**	0.13	0.13	**0.3**
Cold & Flu	2	0	**2**	0.27	0.00	**0.3**
Hot flushes	1	1	**2**	0.13	0.13	**0.3**
Swollen joints	1	0	**1**	0.13	0.00	**0.1**
Suffocating	0	1	**1**	0.00	0.13	**0.1**
Urine discoloration	0	1	**1**	0.00	0.13	**0.1**
Neck pain	0	1	**1**	0.00	0.13	**0.1**
Toothache	0	1	**1**	0.00	0.13	**0.1**
Night sweat	1	0	**1**	0.13	0.00	**0.1**
Sore dry throat	0	1	**1**	0.00	0.13	**0.1**
Fever	0	1	**1**	0.00	0.13	**0.1**

Table 4: Comparative data of side-effects reported or medical consultation required after single dose or multiple dose administration

	Single Dose	Multiple Dose	Missing data	TOTAL
Participants	741	702	94	1537
Side-effects reported	179	189	24	392
Medical Consultation	40	36	2	78

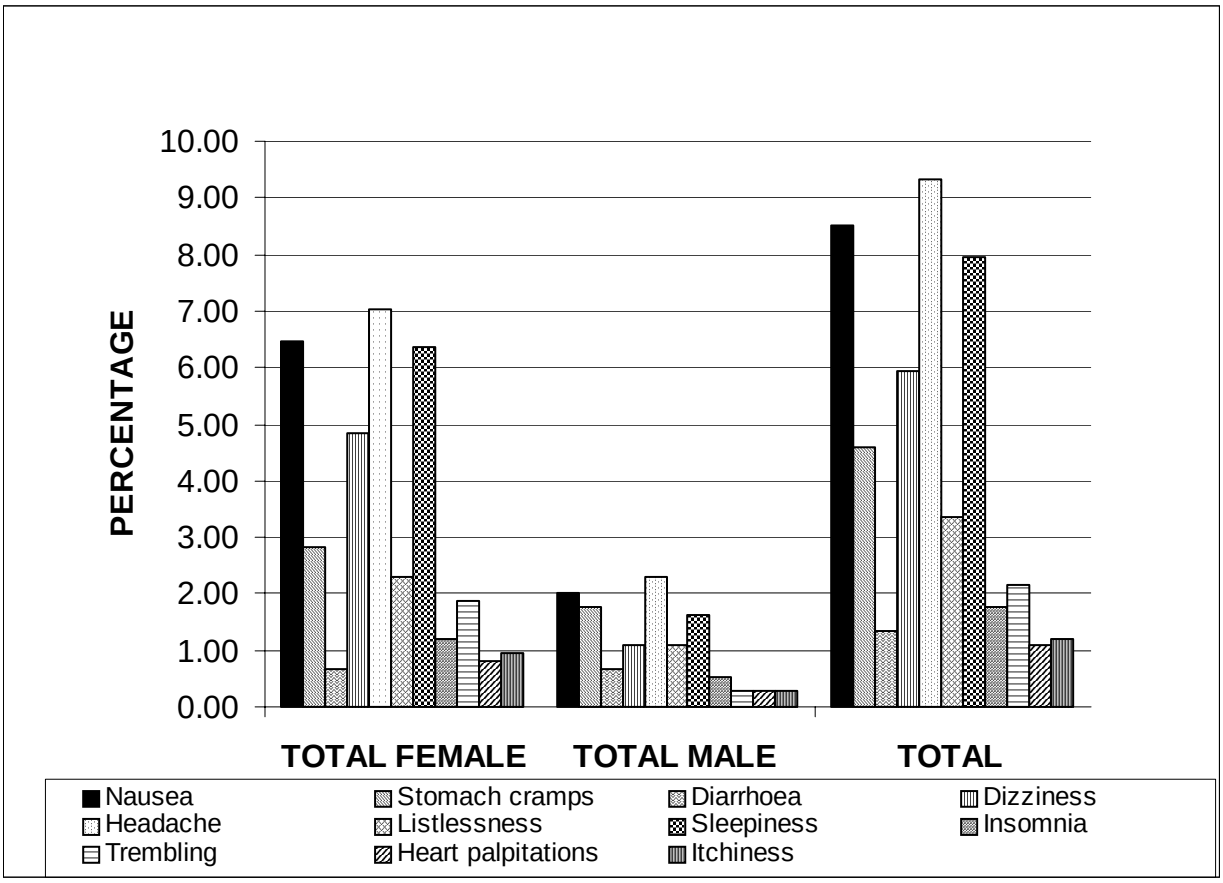

Figure 1: Percentage of total side-effects reported > 1% (Single Dose)

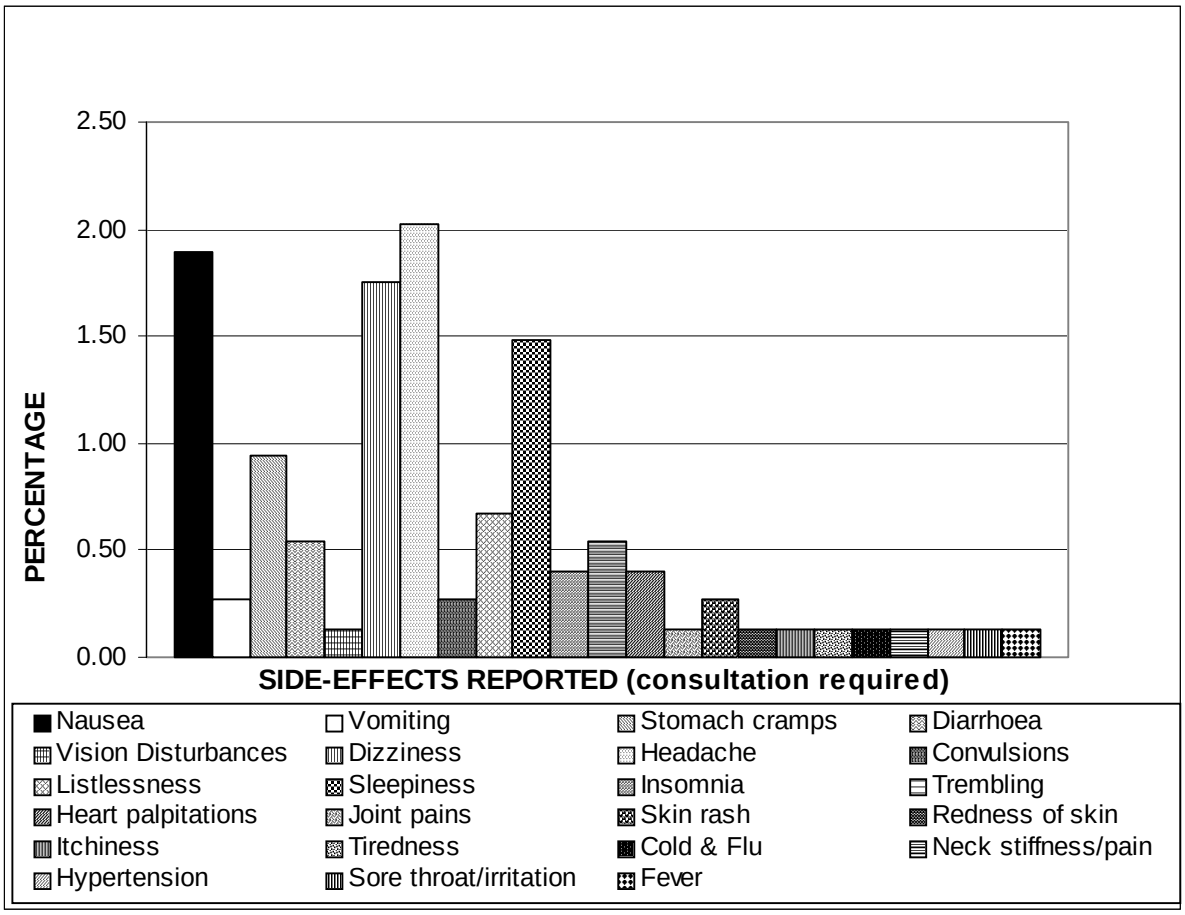

Figure 2: Percentage of the side-effects for which consultation was required (Single Dose)

pants that only 51.4% (n=1443,94 missing data) of the participants took a single dose of ciprofloxacin 500 mg. The remaining 48,6% took more than one dose of ciprofloxacin 500 mg.

The total percentage of participants who reported side-effects was 25.5% (392 participants) of the 1537 voluntary participants, but this included both the single dose and multiple dose groups. Side-effects resulting from multiple doses compared to side-effects resulting from a single dose did not indicate any practical significance. The side-effects reported by the single dose participants were 24.2% (expressed as a percentage of the total number of participants, 741, on single dose only) and by the multiple dose participants 26.9% (expressed as a percentage of the total number of participants, 702, multiple doses).

The participants requiring further medical consultation due to the severity of their side-effects after a single dose of ciprofloxacin 500 mg totalled 5.4% (expressed as a percentage of 741 participants). When the effect size (w) was calculated and compared to the guidelines as provided by Cohen (1988) no practically significant relationship was shown for any of the side-effects reported on single dose, multiple doses, nor when the effects of gender or requirement for medical consultation were tested.

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ADDENDUM:

VOLUNTARY QUESTIONNAIRE WITH REGARD TO THE MENINGITIDIS PREVENTATIVE PROJECT

Dear Staff member / Student

In light of the current events the last couple of weeks concerning the meningitis outbreak in Potchefstroom, the pharmacologists and pharmacists of the School of Pharmacy of PU for CHE request your cooperation with the completion of the following questionnaire. The prophylactic medication used was ciprofloxacin 500 mg (also known as Ciprobay®; Adco-Cifrin®; Cifloc®; Cifran®) provided to you as a single dose on 28 July 2003. Children would have received according to their age smaller doses of ciprofloxacin or even rifampicin as supplied by retail pharmacies; state hospitals or clinics. Ciprofloxacin is currently accepted worldwide as the most suitable oral drug for prophylaxis of *Neisseria meningitidis* in adults, despite several possible side effects as described in the pharmacological literature. We are of the opinion that you can assist us to obtain useful information regarding the **actual** side-effects of a single ciprofloxacin dose, as experienced by this specific target population. Information gained from the Potchefstroom experience may be valuable in future - not only for Potchefstroom residents, but also for the management of similar outbreaks in other communities. Your friendly and voluntary cooperation in completing this questionnaire is therefore much appreciated. All information will be treated confidentially.

Please mark the relevant space clearly with a cross (x) and provide more detailed information only when requested. If a specific question is not relevant just ignore it.

1. **Participant:**

1.1	Personnel	
1.2	Student, living OFF-CAMPUS	
1.3	Student, living ON-CAMPUS in university residence	
1.4	Other	

2. Age in years :

3. Gender:

Female	Male

4. If you are a female, are you

4.1	Pregnant	
4.2	Breast feeding	

5. Time (e.g. 17:00; 18:00; 20:15) of ingestion of the medication on 28 July 2003:

6. Where did you receive your medication from?

6.1	PUK Campus	
6.2	Potchefstroom Hospital	
6.3	Municipal clinics	
6.4	Retail pharmacies	
6.5	Other	

		YES	NO
7.	Did you experience any side-effects or any strange reactions **within 24 hours** after taking the medication, in other words any effects that you are not normally aware of? ***(Please complete questions 11-14 even if your response here is NO.)***		

8. If you have responded YES to question 7, please mark (x) which type of side-effect had been experienced in the column provided next to the relevant side-effect:

8.1 Nausea		8.7 Headache		8.13 Heart palpitations	
8.2 Vomiting		8.8 Convulsions		8.14 Joint pains	
8.3 Stomach cramps		8.9 Listlessness		8.15 Swollen joints	
8.4 Diarrhoea		8.10 Sleepiness		8.16 Skin rash	
8.5 Visual disturbances		8.11 Insomnia		8.17 Redness of the skin	
8.6 Dizziness		8.12 Trembling		8.18 Itchiness	

9. List any other symptoms or side-effects that you have experienced within 24 hours of taking the medication.

.....

		YES	NO
10.	Did you consult a doctor; pharmacist or nurse with regard to the side-effects you have experienced?		
11.	Are you currently using any of the following **chronic medication** (on a regular daily basis):		
11.1	Theophylline (eg Theoplus®; Uniphyl®; Theophen®; Euphyllin Retard®; Microphyllin®).		
11.2	Anti-inflammatory drugs for example Aspirin (Disprin®); Ibuprofen (Brufen®; Inza®); Diclofenac (Voltaren®; Panamor®); Indomethazine (Indocid®; Arthrexin®); Piroxicam (Feldene®); Ketoprofen (Orucote®; Ketoflam®); Naproxen (Naprosyn®; Nafasol®); Flurbiprofen (Froben®); Celecoxib (Celebrex®); Meloxicam (Mobic®); Rofecoxib (Vioxx®).		
11.3	Warfarin		
11.4	Anti-epileptic drugs (specify).		
11.5	Anti-diabetic drugs (specify).		
11.6	Anti-asthmatic drugs (specify).		

12. List any other medication that you are currently using on a regular daily basis that are not listed above.....

		YES	NO
13.	Have you taken any prophylactic medication against meningitis, during the month of July 2003, prior to this mass action that took place on 28 July 2003?		

14. If you have responded **YES**, to question 13, please provide the following information if you can recall it.

14.1	Date medication was used	
14.2	Name of medication used	
14.3	What was the dosage and quantity?	
14.4	Place where you obtained the medication?	

Thank you very much for your friendly cooperation in this investigation. We would appreciate it very much if you could deliver the completed questionnaire to us before or on Wednesday 6 August 2003.

Personnel and students are requested to make use of the intern mail delivery system to:

Ciprofloxacin Study, Department of Pharmacology, Bussie 16. Alternatively return it by e-mail or hand it to the designated student representative of your residence.

Any inquiries regarding this questionnaire can be made to Michelle Viljoen (fklmv@puknet.ac.za) at 299-2232 or Rina Meyer (fklclm@puknet.ac.za) at 299-2228 or 018 299-2226.