Pattern of Mefloquine Ingestions Reported to Texas Poison Centers

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Abstract

Background. Mefloquine is an antimalarial drug available in the United States that in 2013 was given a black box warning about the potential for neurologic and psychiatric adverse effects. **Objective.** This study describes mefloquine ingestions reported to a large statewide poison center system. **Methods.** The distribution of all mefloquine ingestions reported to Texas poison centers during 2010 to 2014 was determined for dose, year, patient age and gender, exposure site, ingestion reason, management site, medical outcome, clinical effects, and treatments. **Results.** Of 63 total cases, the mean dose was 672 mg (range = 188–3500 mg). The patient age distribution was 5 years or less (27.0%), 6 to 19 years (12.7%), and 20 years or more (58.7%); 52.4% of the patients were male. Therapeutic errors accounted for 71.4% of the cases and adverse reactions 19.0%. The management site was 52.4% on site, 19.0% already at/en route to a health care facility, and 23.8% referred to a health care facility. The medical outcome was not serious in 79.4% of the cases. The most common adverse effects were gastrointestinal (28.6%) or neurological (20.6%) in nature. One case each was reported to have depression, paranoia, and almost psychotic presentation. **Conclusions.** Few mefloquine ingestions were reported to Texas poison centers. Those that were reported tended to involve adult males and were due to therapeutic error or adverse reaction. Although mefloquine ingestions may result in potentially serious side effects, the exposures reported to Texas poison centers tended not to be serious with few adverse effects and were managed outside of health care facilities.

Keywords

antimalarial drug, mefloquine, poison center, management, outcome

Introduction

Mefloquine is an antimalarial drug belonging to the quino-lone-methanol group and a quinine analog developed in the 1970s by the US Department of Defense. The drug is used in the prevention and treatment of uncomplicated drug-resistant *Plasmodium falciparum* malaria. The exact mechanism of action of mefloquine is unknown; however, it is thought to operate via the destruction of the asexual intraerythrocytic forms of the human malaria parasite *P falciparum*. The recommended adult dose for prophylaxis is 250 mg taken once a week. Mefloquine is available in 250 mg tablets.¹

In August 2009, Hoffmann-La Roche stopped marketing Lariam (Hoffmann-La Roche Ltd, Basel, Switzerland) in the United States. However, generic versions of mefloquine are still available. In 2013, mefloquine was the third most prescribed antimalarial drug in the United States. Approximately 119 000 prescriptions were written for mefloquine during January to June 2013, compared to 2.4 million prescriptions for hydroxychloroquine, the most commonly used antimalarial drug (although it should be noted that hydroxychloroquine may be prescribed for other indications such as rheumatoid arthritis).²

Adverse clinical effects reported with mefloquine use include gastrointestinal events (diarrhea, nausea, abdominal pain, vomiting), nervous system disorders (headache, dizziness), and cardiovascular disorders (chest pain, tachycardia, palpitation, bradycardia, irregular heart rate, hypotension, hypertension).¹ Psychiatric side effects such as anxiety, panic attacks, paranoia, delusions, psychosis, violence, and suicide with mefloquine use have been reported in the literature.^{1,3} The US Food and Drug Administration (FDA) reviewed mefloquine adverse event reports from its Adverse Event Reporting System. Following that review, the FDA announced that a black box warning should be added to the drug label because of the neuropsychiatric adverse effects associated with the drug.⁴ Subsequently, the Surgeon General's Office of the Army Special Operations Command ordered a halt to the prescribing of mefloquine to special operations forces.⁵

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US poison centers are telephone consultation services that provide information on and assist in the management of potentially adverse exposures to a variety of substances and poisons. Calls are received from the public, law enforcement, and health care providers. The objective of this investigation was to describe mefloquine exposures reported to a large statewide poison center system and particularly noting whether any neurological effects such as reported in the literature were observed.

Materials and Methods

The data source for this retrospective study was the Texas Poison Center Network (TPCN), a system of 6 poison centers that together serve the entire state with a current population of over 25 million. The 6 poison centers use a single, common electronic database to collect demographic and clinical information on all calls in a consistent manner. The data fields and allowable data options are standardized by the American Association of Poison Control Centers.⁶

Cases were mefloquine ingestions reported to the TPCN during 2000 to 2014. Ingestions involving other substances in addition to mefloquine were included. Cases not followed to a final medical outcome also were included. However, it is understood that information on cases not followed to a final medical outcome, particularly clinical effects and treatments, might be incomplete. Calls from outside of Texas were excluded.

The distribution of the cases was determined for dose ingested, presence of coingestants, year, patient age and gender, exposure site, circumstances of (reason for) the ingestion, management site, medical outcome, adverse clinical effects, and treatment received. Because of the small number of cases, analysis of statistical significance were not performed. The dose ingested was based on information provided by the caller and not independently confirmed by toxicological analysis.

The medical outcome or severity of an exposure is assigned by the poison center staff and is based on the observed or anticipated adverse clinical effects. Medical outcome is classified according to the following criteria: no effect (no symptoms due to exposure), minor effect (some minimally troublesome symptoms), moderate effect (more pronounced, prolonged symptoms), major effect (symptoms that are life-threatening or cause significant disability or disfigurement), and death. A portion of exposures are not followed to a final medical outcome because of resource constraints or the inability to obtain subsequent information on the patient. In these instances, the poison center staff record the expected outcome of the exposure. These expected outcomes are grouped into the following categories: not followed but judged as nontoxic exposure (symptoms not

expected), not followed but minimal symptoms possible (no more than minor symptoms possible), unable to follow but judged as a potentially toxic exposure. Another medical outcome category is unrelated effect where the exposure was probably not responsible for the symptoms.

The adverse clinical effects are coded in 131 check-boxes specific to particular clinical effects, and therapies are coded in 68 check-boxes specific to particular treatments. A clinical effect or treatment that cannot easily be assigned to a specific check-box is assigned to the "other" check-box. This is important for the present investigation because some of the adverse clinical effects of great concern with mefloquine ingestion, such as depression and paranoia, do not have corresponding specific check-boxes. Clinical effects and treatments also may be recorded in the Notes field of the TPCN database. However, a previous investigation has indicated that all of the clinical effects and treatments recorded in the Notes field are not also recorded in the check-boxes and vice versa.⁷ The Notes fields of all of the cases were reviewed for reported adverse clinical effects, particularly those of a psychological nature.

The Texas Department of State Health Services institutional review board considers this analysis exempt from ethical review.

Results

Sixty-three mefloquine ingestions met the study criteria. The dose ingested was reported for 58 cases. The mean dose was 672 mg (range = 188-3500 mg). Other substances were reported in 3 (4.8%) of the ingestions (2 ciprofloxacin ingestions and 1 mercaptopurine ingestion).

The annual number of reported ingestions ranged from 1 to 9 cases with no apparent trend. The distribution of cases by patient age was 17 (27.0%) 5 years or less (mean dose = 351 mg, range = 188-1750 mg), 8 (12.7%) 6 to 19 years (mean dose = 893 mg, range = 250-1750 mg), 37 (58.7%) 20 years or greater (mean dose = 787 mg, range = 250-3500 mg), and 1 (1.6%) unknown age. Thirty-three (52.4%) of the patients were male (mean dose = 553 mg, range = 188-1750 mg) and 30 (47.6%) were female (mean dose = 782 mg, range = 220-3500 mg).

The ingestion was reported to have occurred at the patient's own residence in 60 (95.2%) cases (mean dose = 686 mg, range = 188-3500 mg), another residence in 2 cases (3.2%), and the workplace in 1 case (1.6%). The ingestion was reported to have involved therapeutic error in 45 (71.4%) cases (mean dose = 716 mg, range = 188-3500 mg) and adverse drug reaction in 12 (19.0%) cases (mean dose = 528 mg, range = 250-1250 mg). Other reported reasons for the ingestion were unintentional-general ($n = 2$), unintentional-unknown ($n = 1$), suspected attempted suicide ($n = 1$), intentional misuse ($n = 1$), and unknown reason ($n = 1$).

Table 1. Mefloquine Ingestions Reported to the Texas Poison Center Network During 2000 to 2014 by Selected Factors.

Factor	Number	Percent	Mean Dose (mg)	Range (mg)
Management site				
On site (non-health care facility)	33	52.4	617	250-1750
Referred to health care facility	15	23.8	388	188-1250
Already at/en route to health care facility	12	19.0	1028	250-3500
Other (unspecified)	2	3.2	1500	1250-1750
Unknown	1	1.6	250	-
Medical outcome				
No effect	8	12.7	332	188-1000
Minor effect	7	11.1	714	250-1750
Moderate effect	3	4.8	1375	1250-1500
Not followed, judged nontoxic	4	6.3	625	250-1250
Not followed, minimal effect possible	31	49.2	783	250-3500
Unable to follow, potentially toxic	9	14.3	385	250-750
Unrelated effect	1	1.6	250	
Total	63		672	188-3500

Table 1 shows the distribution of mefloquine ingestions by management site and medical outcome. Most of the patients were managed on site (outside of a health care facility). The mean dose ingested for patients managed on site was lower than that for patients already at or en route to a health care facility when the poison center was contacted but higher than that for patients referred to a health care facility by the poison center. Fifty (79.4%) of the ingestions resulted in outcomes that were not serious (no effect, minor effect, not followed and judged nontoxic, or minimal effect possible; mean dose = 687 mg, range = 188-3500 mg), and 12 (19.0%) resulted in potentially serious outcomes (moderate effects, unable to follow but potentially toxic; mean dose = 633 mg, range = 250-1500 mg). No major effects or deaths were reported.

Table 2 presents the specific adverse clinical effects reported with mefloquine ingestions. The clinical effects tended to be gastrointestinal and neurological in nature. Review of the record notes found one patient was reported to be experiencing depression, another paranoia, and a third almost psychotic presentation. Table 3 provided details on the cases with moderate outcomes or psychiatric affects.

Almost all of the specific treatments that were reported were some form of decontamination (Table 4).

Discussion

Only a small number of potentially adverse exposures to mefloquine were reported to Texas poison centers from a population of over 25 million during a 15-year period. No annual trend in reported exposures was observed; in particular, the number did not decline after 2009, when Lariam was no longer marketed in the United States, nor after 2013, when the FDA added a black box warning to mefloquine.⁴

Table 2. Adverse Clinical Effects Reported With Mefloquine Ingestions Reported to the Texas Poison Center Network During 2000 to 2014.

Clinical Effect	Number	Percent	Mean Dose (mg)	Range (mg)
Cardiovascular	4	6.3	583	250-1250
Chest pain	2	3.2	250	
Hypertension	1	1.6		
Tachycardia	1	1.6	1250	
Dermal	1	1.6	250	
Edema	1	1.6	250	
Pruritus	1	1.6	250	
Rash	1	1.6	250	
Gastrointestinal	18	28.6	837	250-3500
Abdominal pain	4	6.3	875	250-1750
Anorexia	2	3.2	281	250-313
Constipation	1	1.6	250	
Diarrhea	4	6.3	1688	500-3500
Nausea	7	11.1	929	250-3500
Throat irritation	1	1.6	250	
Vomiting	4	6.3	563	250-1250
Neurological	13	20.6	705	250-3500
Agitation	4	6.3	750	250-1750
Confusion	3	4.8	500	
Dizziness	6	9.5	1125	250-3500
Hallucinations	1	1.6	1500	
Headache	4	6.3	1500	250-3500
Respiratory	1	1.6	250	
Dyspnea	1	1.6	250	
Miscellaneous	13	20.6	1023	250-3500
Bleeding	1	1.6	250	
Diaphoresis	1	1.6	1250	
Fever	2	3.2	750	250-1250
Pain	2	3.2	250	
Other (unspecified)	9	14.3	964	250-3500
Total	63		672	188-3500

Table 3. Patients With Moderate Effects or Psychological Effects After Mefloquine Ingestion Reported to the Texas Poison Center Network During 2000 to 2014^a.

Demographics	Dose (mg)	Circumstances	Medical Outcome	Management Site	Clinical Effects
Male, 26 years	1500	Therapeutic error	Moderate effect	Health care facility	Diarrhea, hallucinations, paranoia
Male, 64 years	1250	Intentional misuse	Moderate effect	On site	Tachycardia, diarrhea, diaphoresis, fever
Male, 17 years	Unknown	Adverse reaction	Moderate effect	Health care facility	Hypertension, agitation (almost psychotic presentation), confusion, headache
Male, adult	Unknown	Adverse reaction	Unable to follow—potentially toxic	Referred to health care facility	Depression

^aNone of these patients were reported to have coingestants.

Table 4. Treatments Reported With Mefloquine Ingestions Reported to the Texas Poison Center Network During 2000 to 2014.

Treatment	Number	Percent	Mean Dose (mg)	Range (mg)
Activated charcoal	1	1.6	220	
Cathartic	1	1.6	220	
Dilution	9	14.3	479	250-1750
Food/snack	4	6.3	641	250-1750
Antiemetics	1	1.6	3500	
Benzodiazepines	1	1.6		
Other (unspecified)	13	20.6	813	250-3500
Total	63		672	188-3500

The number of mefloquine prescriptions in Texas during the same time period is not known, so comparisons cannot be made.

The majority of patients were adults, although the next highest proportion were young children. The mean reported dose was lower for young children than for adults. The most common circumstance for the mefloquine ingestion was therapeutic error followed by adverse drug reaction. As might be expected, the mean dose for therapeutic errors was higher than that for adverse reactions. In comparison, of the 1 327 321 total drug-related exposures reported to the TPCN during 2000 to 2014, 260 360 (19.6%) involved therapeutic errors. This might suggest that mefloquine may be associated with more therapeutic errors than a number of other drugs. This may be because the recommendation for mefloquine prophylaxis is that the drug be taken once a week; individuals might mistakenly take mefloquine more frequently.

The preponderance of the ingestions did not result in potentially serious effects. Of note, the mean dose for serious outcomes (633 mg) was slightly lower than that for outcomes that were not serious (687 mg). As a consequence of most of the ingestions not resulting in serious outcomes, it

might be expected that most patients would be managed outside of health care facilities. Over half of the patients were managed on site. It should be indicated that while the mean dose for patients managed on site was lower than that for patients already at or en route to a health care facility, it was actually higher than the mean dose for patients referred to a health care facility by the poison center.

Patients were most frequently reported to have gastrointestinal effects followed by nervous system effects with cardiovascular effects reported in only 4 cases. The particular adverse effects were consistent with those reported previously.¹ Psychiatric effects of particular concern (anxiety, panic attacks, paranoia, delusions, psychosis, violence, etc)^{1,3,4} were reported in only 3 patients.

This investigation is subject to various limitations. Reporting of potentially adverse mefloquine ingestions to Texas poison centers is voluntary. As a result, it is not expected that all such ingestions are reported, and those that are reported might not be representative of all potentially adverse ingestions. In addition, this study included a small number of cases; further studies with larger data sets would be useful.

As noted in the methodology, the dose was based on caller reports and not determined by toxicological analysis. Moreover, only a fraction of the cases were followed to a final medical outcome. Thus, the documentation of clinical information, including clinical effects and treatments, might be incomplete. Finally, the clinical effects of particular concern with mefloquine use, such as depression and paranoia, could not easily be recorded in the TPCN's database checkboxes and may not have been recorded in the record notes. As a result some cases involving these clinical effects might have been missed.

In summary, few mefloquine ingestions were reported to Texas poison centers. Those that were reported tended to involve adult males and were due to therapeutic error or adverse reaction. Although mefloquine ingestions may result in potentially serious side effects, the exposures reported to Texas poison centers tended not to be serious

with few adverse effects and were managed outside of health care facilities. Still, poison centers need to be aware for the potential of serious psychological effects when managing mefloquine ingestions.

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