MAJOR ARTICLE

US Food and Drug Administration Approval of Ciprofloxacin Hydrochloride for Management of Postexposure Inhalational Anthrax

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In August 2000, the US Food and Drug Administration (FDA) approved ciprofloxacin hydrochloride (Cipro; Bayer) for management of postexposure inhalational anthrax. This was the first antimicrobial drug approved by the FDA for use in treating an infection due to a biological agent used intentionally. The terrorist attacks of 2001 involving anthrax underscore the imperative that safe and effective drugs to manage such infections be readily available in the United States. The approval of ciprofloxacin hydrochloride, which was made on the basis of a surrogate human marker of efficacy, made extensive use of data from an animal model of disease. This represents a new direction in the development of efficacy data in support of drug approval and facilitates the availability of those drugs for which there is an urgent need. This article presents the scientific data and regulatory mechanism that supported the approval of ciprofloxacin hydrochloride for management of postexposure of inhalational anthrax.

In August 2000, the US Food and Drug Administration (FDA) approved ciprofloxacin hydrochloride (Cipro; Bayer; hereafter, ciprofloxacin) for management of postexposure inhalational anthrax. This was the first antimicrobial drug approved by the FDA for treating infection due to a biological agent used intentionally. The anthrax attacks of 2001 underscore the imperative that safe and effective drugs to treat such infections be readily available in the United States. The approval of ciprofloxacin, made on the basis of a surrogate human marker of efficacy, made extensive use of data from an animal model of disease. This represents a new direction in the development of efficacy data used in support of drug approval. This report is an account of the data used in making a federal regulatory decision of significant public health importance. Its purpose is to provide to the infectious diseases community the data used in making a regulatory decision in the context of a response to a public health emergency. It is an effort to more fully inform clinicians of the data they may employ in decision-making and to elucidate for the scientific community and industry an approach to regulatory decision-making as efforts proceed to develop new medical countermeasures against biological threats.

Regulatory status of drugs for anthrax. The evaluation of drugs for the management of inhalational anthrax raises a number of issues. Inhalational anthrax is an extremely rare disease. Because of the high mortality associated with it, it cannot ethically be studied in human subjects in circumstances of intentional exposure. Among the biological threat agents, inhalation anthrax is somewhat unique, in that there was an outbreak of this infection in 1979 among the human population of Sverdlovsk in the former Soviet Union. This outbreak, considered the result of an accident at a military microbiology facility, provided one of the few opportunities for systematic study of human disease resulting from any agent that is a biological threat [1, 2].

Consideration of the development of a large-scale use program after a possible exposure to aerosolized spores of *Bacillus anthracis* raises issues of drug resis-

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tance, safety, and compliance with therapy. There have been reports of bioengineered strains of *B. anthracis* resistant to drugs traditionally active against it [3]. In addition, rates of penicillin allergy and gastrointestinal intolerance of the tetracyclines warrant the availability of a choice of agents in the event of a need for drug administration after exposure of a large population to this pathogen.

Ciprofloxacin. Ciprofloxacin in tablet form was approved for human use in the United States in 1987. The approved regimen for oral ciprofloxacin for managing inhalational anthrax after exposure is similar to previously approved dosages, as shown in table 1. At the time of the anthrax approval, ciprofloxacin had been used by 250 million patients worldwide. It was approved for 13 indications, including deep tissue infections, such as lower respiratory tract and complicated intraabdominal infections. It is also approved for a long-term use indication for treating bone and joint infections (⩾4–6 weeks). It is approved for treating typhoid fever, which, like inhalational anthrax, is an infection of the reticuloendothelial system.

CIPROFLOXACIN FOR MANAGEMENT OF POSTEXPOSURE INHALATIONAL ANTHRAX: SUMMARY OF EXPERIMENTAL DATA

The study of ciprofloxacin for prevention of inhalational anthrax was performed in a monkey model. It was conducted at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) in 1990, at the start of the Persian Gulf War, with the purpose of developing a practical regimen for soldiers exposed to *B. anthracis* in field conditions. The results demonstrated a significantly improved survival rate for animals that received ciprofloxacin after exposure to aerosolized *B. anthracis*, compared with controls. Ciprofloxacin serum concentrations were measured in these animals, and it has been shown that these levels are reached or exceeded in human populations that receive ciprofloxacin in the doses recommended for this indication.

***Microbiology of* B. anthracis.** Traditionally, *B. anthracis* is susceptible to drugs of the penicillin and tetracycline classes. Ciprofloxacin is similarly potent in inhibiting the growth of *B. anthracis;* the MIC_{90} of ciprofloxacin is 0.06 μg/mL. Observations from the published literature state that ~3% of naturally occurring anthrax strains are resistant to penicillin [4, 5].

Comparison of animal and human pharmacokinetics. Peak and trough concentrations of ciprofloxacin were obtained from animals studied in the USAMRIID rhesus monkey model of inhalational anthrax. These values can be compared with those obtained from pharmacokinetic studies in adults and children who received ciprofloxacin at the dosages approved for managing postexposure inhalational anthrax. Serum concentrations of ciprofloxacin across these 3 populations were found to be comparable. The maximum concentration (C_{max}) was 1.74 μg/mL for monkeys, 2.97 μg/ml for human adults, and 3.5 μg/mL for human children. The minimum concentration (C_{min}) was 0.17 μg/mL for monkeys and 0.2 μg/mL for human adults and was consistently higher than the MIC_{90} of ciprofloxacin for *B. anthracis* (0.06 μg/mL) [6-10].

Inhalational anthrax: animal models and human pathology. Since the 1940s, studies of inhalational anthrax have been conducted in a number of animal species. The study of human disease resulting from sporadic industrial exposure and from the 1979 outbreak in Sverdlovsk has provided an understanding of inhalational anthrax that demonstrates that the rhesus monkey is a relevant animal model of this disease [2, 3]. The applicability of this model is based on data attesting to the similarities in pathogenesis, clinical course, and tissue pathology in rhesus monkeys and humans with inhalational anthrax.

Animal model: study supporting the indication of ciprofloxacin. The USAMRIID rhesus monkey model was designed to study drug doses that were equivalents of human doses. The study involved 60 monkeys that were exposed to an inhaled dose of ~8 LD_{50} *B. anthracis* Vollum spores. There were 6 groups of 10 animals each. One group received human anthrax vaccine only on days 1 and 14 after exposure. Three groups received a 30-day regimen of antimicrobials that was started 24 h after exposure. The antibiotics administered were penicillin, doxycycline, and ciprofloxacin. One group received both doxycycline and vaccine, and a control group of 10 monkeys received saline intramuscularly. After this exposure, animals were observed for a total of 90 days. All animals had serial blood specimens obtained for culture. Animals that died or were sacrificed underwent necropsy; tissue specimens were cultured and examined histologically [11].

Results were reported as mortality rates or postexposure survival curves [11]. Inspection of the data presented in figure 1 demonstrates markedly different survival curves for the animals that received postexposure ciprofloxacin for 30 days, compared with those animals that received saline control.

Inspection of the survival curves in figure 2 shows the results for all 6 groups of monkeys. The animals in the control and in the postexposure vaccine groups demonstrated a rapid decrease in survival and a high mortality rate, and those that

Table 1. Dosing regimens of ciprofloxacin for management of inhalation anthrax, as approved by the US Food and Drug Administration.

Patient population	Oral regimen	Intravenous regimen
Adult	500 mg q12h × 60 days	400 mg q12h
Pediatric[a]	15 mg/kg q12h × 60 days	10 mg/kg q12h

[a] Ciprofloxacin is approved for pediatric use *only* for the indication of inhalation anthrax.

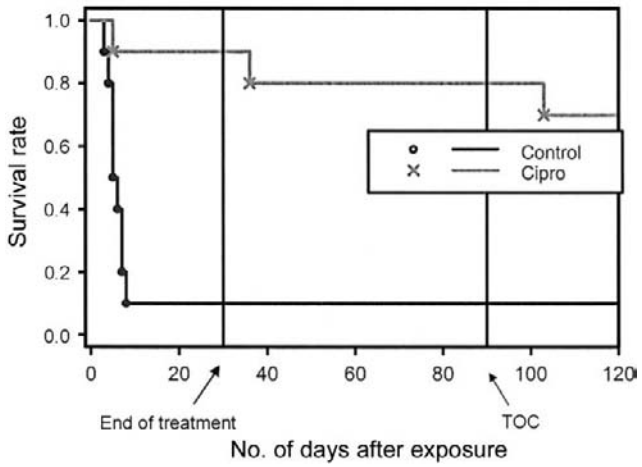

Figure 1. Survival curves for rhesus monkeys administered either ciprofloxacin (Cipro) or saline (Control) after exposure to aerosolized *Bacillus anthracis*. End of treatment occurred at 30 days after exposure; test of cure (TOC) occurred 90 days after exposure. Adapted from [11].

received 30 days of antimicrobial therapy or therapy with antimicrobials plus vaccine demonstrated markedly improved survival. These data suggest that a number of different regimens that were studied in this experiment afford comparable protection after the first challenge.

Table 2 presents a statistical analysis of the mortality rates for animals receiving ciprofloxacin, compared with that for animals in the control group. *P* values demonstrate that, for the evaluable study population, mortality rates for the ciprofloxacin cohort are significantly less than the mortality rate for the control cohort and are similar to mortality rates for the cohorts that received penicillin, doxycycline, or doxycycline plus vaccine.

DURATION OF DRUG ADMINISTRATION

Underlying the consideration of a postexposure regimen of ciprofloxacin was the question of the duration of drug administration. The discussion below describes the approach taken by the FDA in the review of the ciprofloxacin application.

Animal models. Early work by Henderson et al. [12] evaluated the administration of postexposure penicillin in a rhesus monkey model of inhalational anthrax. They hypothesized that inhaled spores were phagocytosed by pulmonary macrophages and transported to the mediastinum, where they germinated and produced toxin. The results of this study [12] are presented in figure 3.

Henderson et al. [12] studied several cohorts of 10 animals, each of which was exposed to aerosolized anthrax spores and subsequently received various regimens of penicillin. Penicillin administration that began 24 h after exposure to aerosolized spores of *B. anthracis* and continued for 5 days was shown to only delay death in the animals exposed (figure 3; group A). When the duration of penicillin therapy was extended to 10 or 20 days, a similar delay of death was observed, and the length of time by which death was delayed was generally proportional to the duration of antimicrobial administration (figure 3; groups B and C).

Henderson et al. [12] noted that only a small proportion of inhaled spores was ultimately deposited in local lymph nodes; other spores were detected in the lung parenchyma 100 days after exposure. Using pathologic specimens, they also quantified the proportion of spores that were found in the lungs after exposure and produced the results presented in table 3.

Thus, the idea of spore attrition was introduced. Small numbers of spores could be found as long as 100 days after exposure. The work of Henderson's group supported the idea of "dormant infection" and demonstrated that a number of antimicrobial regimens were too short to successfully protect the exposed rhesus monkey from inhalational anthrax. These experiments also invoked the concept of "spore clearance," suggesting that there existed a mode of exit from the lung for *B. anthracis* spores other than phagocytosis and subsequent development into the pathogenic vegetative state.

Other early studies of inhalational anthrax in the guinea pig by Ross [13] permitted direct observation of spores that were deposited on pulmonary alveolar epithelium and provided insight into possible mechanisms of spore attrition. Ross [13] noted that the number of spores that reached regional lymph nodes was substantially less than the number of spores deposited on the alveolar epithelium. Using differential staining tech-

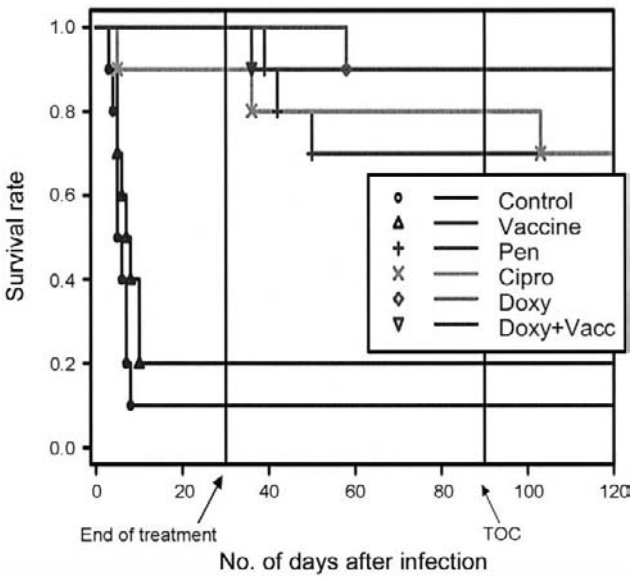

Figure 2. Survival curves for rhesus monkeys administered either penicillin (Pen), ciprofloxacin (Cipro), doxycycline (Doxy), a vaccine (Vaccine), doxycycline plus a vaccine (Doxy + Vacc), or saline (Control) after exposure to aerosolized *Bacillus anthracis*. Adapted from [11].

niques, she provided histological evidence that not all inhaled spores develop into vegetative organisms that produce systemic disease [13].

Early studies by Henderson's group demonstrated that regimens of 5, 10, and 20 days of postexposure antibiotic administration were too short; high mortality rates in the study cohorts were only delayed [12]. Review of the USAMRIID data from the initial challenge phase of the survival curves suggests that a regimen of 30 days results in survival rates that begin to approximate the "best case" results. However, among the animals that received ciprofloxacin, 1 in 10 was not sufficiently protected from inhalational anthrax after 30 days of therapy. This suggests that, after 30 days of antimicrobial therapy, there remained an adequate number of inhaled spores to progress to the vegetative phase, produce toxin, and cause disease. The largest human epidemic of inhalational anthrax ever reported occurred in Sverdlovsk in 1979. Data from this outbreak, for which data from a series of 42 necropsies were reported [1], show that 1 patient developed disease 43 days after the presumed exposure. Given the possibility that there exist(s) some mechanism(s) of spore attrition over time, might there be a "floor" to the spore load in the lung, below which level inhalational anthrax is unlikely to occur? If such a lower limit exists, is there a period of antimicrobial administration that will eradicate enough of the developing vegetative organisms such that the risk of disease is minimized? The discussion below addresses these questions.

Human epidemiology. A rough approximation of spore load according to the amount of time after exposure to aerosolized *B. anthracis* spores is provided in table 3. It suggests that, 50 days after exposure, the number of spores in the lungs is ~2% of the original inhaled load. However, it neither quantifies the spore load nor does it speculate about the number of spores that are sufficient for the development of clinical disease. The findings of epidemiological studies of mill workers with industrial exposure to anthrax spores provide some insight into this question. Air sampling in animal-hair mills has demonstrated that nonimmunized workers inhaled between 150–700 anthrax-contaminated particles with a diameter of $\leqslant 5\ \mu$ during a single 8-h shift, but clinical inhalational anthrax was rare among workers in those mills [14, 15]. Other investigators recovered *B. anthracis* from the nose and pharynx of 14 of 101 healthy workers in 2 goat-hair mills [16]. Thus, the possibility exists that there is a low organism load that is not associated with clinical disease.

One might consider repeated low-level exposures in the workplace a different immunological challenge than that resulting from an intentional exposure to aerosolized anthrax spores. Perhaps the occupational exposures present enough antigen to elicit a protective immune response over time. Epidemiological studies suggest that this is not the case. Brachman and Fekety [17] compared the length of employment in goat-hair processing mills of a group of employees without a history of anthrax with that of a group of employees who had a history of anthrax. They found that the likelihood of the development of anthrax was independent of the length of time of employment in the mill. This suggested that more-prolonged employment (i.e., repeated low-level occupational exposure) was unlikely to be a confounding variable in the assessment of disease-risk from repeated low-level exposure to aerosolized spores [17].

Table 2. Evaluable population analysis for proven cases of death due to anthrax in a rhesus-monkey model.

Treatment group	No. of anthrax-related deaths[a]	P[b]
Control	9/10	…
Vaccine	8/10	>.1
Penicillin	3/10	.0198
Ciprofloxacin hydrochloride	1/9[c]	.0011
Doxycycline	1/10	.0011
Doxycycline plus vaccine	0/9[d]	.0001

[a] Data are no. of deaths due to anthrax/no. of animals in the specified treatment group.

[b] P value versus control, calculated using a 2-tailed Fisher's exact test.

[c] One animal (T292) died 5 days after exposure from aspiration pneumonia, had no evidence of anthrax at autopsy, and was excluded from the evaluable population for this analysis. Another animal (B7388), included in the evaluable population, died 73 days after receiving antibiotic treatment. The cause of death in this animal was believed to be unrelated to the disease and, therefore, this animal was not counted as having experienced death due to anthrax.

[d] One animal (H538) died 6 days after discontinuing doxycycline treatment and showed no evidence of anthrax on autopsy. The cause of death remains unknown; the animal was excluded from this statistical analysis.

The possibility exists that a relatively small load of inhaled anthrax spores could be carried asymptomatically by the unimmunized human host. The eradication of vegetative organisms that results from the administration of ciprofloxacin and from clearance of inhaled, dormant spores raises the question of the appropriate duration of drug administration after exposure to aerosolized spores of *B. anthracis.*

The administration of an antimicrobial agent after exposure to an aerosol challenge is an effort to reduce the risk of development of clinical disease. The experimental and epidemiological data cited above suggest that a prophylactic regimen given after exposure to aerosolized *B. anthracis* should be administered for $\geqslant 45$ days. At some point after that period, the organism load in the lung exceeds a threshold below which the development of disease is unlikely. The duration proposed and approved for the administration of ciprofloxacin after exposure to aerosolized anthrax spores was 60 days, which was twice as long as the 30-day regimen used in the USAMRIID study in which animals demonstrated a significantly improved rate of survival.

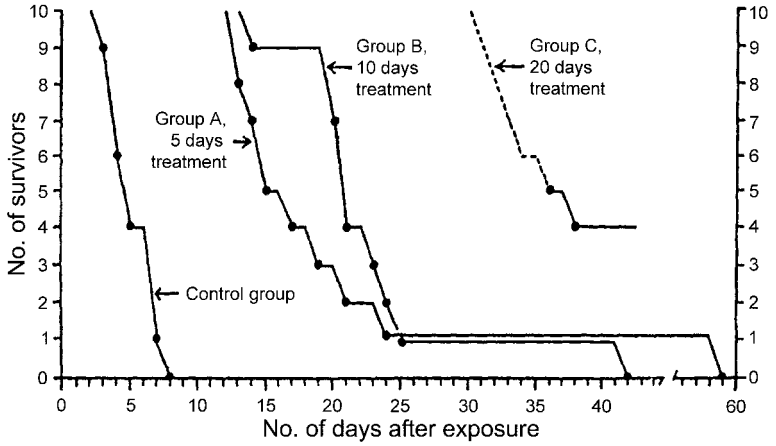

Figure 3. Survival curves for rhesus monkeys administered either penicillin or saline after exposure to aerosolized *Bacillus anthracis*. The control group received saline. Adapted from [12].

CIPROFLOXACIN SAFETY PROFILE

Consideration of a postexposure regimen for inhalational anthrax warranted attention to both prolonged use (for ⩾30 days) and pediatric use.

Prolonged use. A published review [18] provided information on a total of 1049 patients who received ciprofloxacin for ⩾80 days. Adverse events occurred with similar frequency in both the ciprofloxacin group and the comparator groups of the studies. The most common adverse events were gastrointestinal in nature, and no previously unidentified adverse events were noted [18, 19].

Pediatric use. The fluoroquinolone class of drugs has been associated with cartilage abnormalities in experimental juvenile animals, and the safety of drugs of this class has not been established in children. Compassionate use programs for pediatric patients and off-label use by pediatricians have provided some safety data regarding ciprofloxacin use in this population. These data were published in a review [20] that reported safety information for 1795 pediatric patients. Arthralgia occurred in 1.5% of patients. Of these episodes, >60% were seen in children with cystic fibrosis, a disease which can be associated with arthropathy. Hampel et al. [20] cited a previously published report that arthralgia occurred in 1.3% of pediatric patients who received ciprofloxacin. Except for the arthralgia reported, the adverse-event profile in pediatric patients appeared quite similar to that seen in adults [20].

At the meeting of the Anti-infective Drugs Advisory Committee on 28 July 2000, Bayer provided additional safety information regarding the pediatric use of ciprofloxacin [21]. They provided comparative safety data for 167 pediatric patients who received ciprofloxacin and 178 who received a comparator in controlled clinical trials. Arthralgia was less common among children in the ciprofloxacin group, and joint disorders were almost equally common in the 2 groups (5% in the ciprofloxacin group vs. 6% in the comparator group). Bayer reported that, during the past 13 years, ~4.5 million pediatric patients have received ciprofloxacin [19].

The approval of ciprofloxacin for management of postexposure inhalational anthrax included the pediatric population. It was determined that the benefit afforded by the drug to those exposed to aerosolized anthrax spores outweighed the risk quantified by the available safety data.

CIPROFLOXACIN FOR MANAGEMENT OF POSTEXPOSURE INHALATIONAL ANTHRAX: SUMMARY OF REGULATORY ACTION

Inhalational anthrax, a rare and lethal infection that could not be studied prospectively in humans, was studied in an established nonhuman primate model of the disease. Human pathologic findings from the Sverdlovsk outbreak demonstrated that this animal model closely parallels disease in humans. Improved survival of experimental animals in such a model has been demonstrated with the postexposure administration of ciprofloxacin. Serum concentrations of ciprofloxacin shown to correlate with improved survival in this animal model can be

Table 3. Retention of *Bacillus anthracis* spores in the lung after aerosol challenge in a rhesus-monkey model.

Time after exposure, days	Estimated spore retention, % of original amount
42	15–20
50	2
75	0.5–1
100	Trace

NOTE. Subjects were challenged with 2–8 × 10^5spores/L. Adapted from [12].

reached or exceeded in human populations, including adults and children. Ciprofloxacin serum concentrations in humans serve as a surrogate end point for the efficacy of ciprofloxacin in treating postexposure inhalational anthrax. Therefore, the efficacy data in the ciprofloxacin application met the criteria for FDA approval under the accelerated approval (subpart H) regulations [21].

Ciprofloxacin has been used widely and has a well-characterized safety profile. There also exists a significant body of pediatric safety data. The availability of a suitable animal model for inhalational anthrax, the demonstration of a significant survival advantage for experimental animals that received ciprofloxacin, the use of ciprofloxacin serum concentrations in humans as a surrogate end point, the well-established body of safety data for this drug, and the unanimous concurrence of the Anti-infective Drugs Advisory Committee constituted the scientific basis for this approval for use in adult and pediatric populations [19].

CONCLUSION

In August 2000, the FDA approved ciprofloxacin for management of postexposure inhalational anthrax. Data supporting this regulatory action were developed in a primate model of disease. The US anthrax outbreak of 2001 demonstrated the urgent need for safe and effective drugs to treat individuals exposed to biological agents used intentionally. The scientific data and regulatory mechanisms that supported the approval of ciprofloxacin for postexposure inhalational anthrax are an example of a new direction in efficacy evaluation of drugs—the use of animal models of diseases that cannot be studied in humans. These data are presented to illustrate this new direction, undertaken to meet a public health need. Physicians, investigators, and patients are best prepared for public health emergencies such as the recent anthrax outbreak when there is a thorough understanding of the available medical countermeasures.

Acknowledgments

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