

US EPA ARCHIVE DOCUMENT

EPA Ethics Reviews of Completed 4-Aminopyridine Studies

This PDF document includes EPA ethics reviews of the following reports of completed pre-rule studies with 4-Aminopyridine:

Grijalva, I., *et al.* (2003) Efficacy and Safety of 4-Aminopyridine in Patients With Long-Term Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Trial. *Pharmacotherapy* 23(7):823-834. MRID 47093601.

Segal, J., *et al.* (1999) Safety and Efficacy of 4-Aminopyridine in Humans with Spinal Cord Injury: A Long-Term, Controlled Trial. *Pharmacotherapy* 19(6):713-723, 1999. MRID 47093602.

Van Diemen, H., *et al.* (1993) 4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety. *Clinical Neuropharmacology* vol. 16 No. 3, pp. 195-204. MRID 47093603.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MAY 25, 2007

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of 4-Aminopyridine Human Study

FROM: John M. Carley
Human Research Ethics Review Officer

TO: Ray Kent, Chief
Reregistration Branch 4, HED

REF: Grijalva, I., *et al.* (2003) Efficacy and Safety of 4-Aminopyridine in Patients With Long-Term Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Trial. *Pharmacotherapy* 23(7):823-834. MRID 47093601.

This review characterizes the ethical conduct of the research reported in the referenced document in terms of the ethical standards which prevailed when the study was performed. The review applies a variant of the "Summary Framework for Ethical Assessment" developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached.

This study was conducted in Mexico in 1999-2000 at the Instituto Mexicano del Seguro Social in Mexico City. This institution has a registered IRB and holds a Federal-Wide Assurance from OHRP, and the Common Rule was the prevailing standard applicable to this research.

A. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the study under the seven headings used in the attached framework. Supporting details are in the attachment.

- 1. Value of Research to Society:** This report describes a randomized, placebo-controlled, double-blind crossover study in 27 non-pregnant adult out-patients with traumatic spinal cord injury of at least 1.5 years' duration. This paper reports improvements in the patients' condition with some side effects but no significant associated drug toxicity. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.
- 2. Scientific Design:** I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.
- 3. Subject Selection:** 21 men and 4 non-pregnant women with traumatic spinal cord injuries of at least 1.5 years' duration completed the study. Two additional subjects (sex not reported) began the study but did not complete it; three more withdrew late in the study, but their results were included in the analysis. Age range of subjects was 23-48 years. The means by which subjects were recruited are not reported. Before enrolling, each participant underwent a comprehensive clinical evaluation. Exclusion criteria included pregnancy or lactation. There is no indication that subjects were recruited on any basis other than the scientific goals of the study.
- 4. Risks and Benefits:** Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. This research was undertaken to explore longer-term exposures to daily 4-AP and the potential for lasting effects after discontinuation of 4-AP treatment. Subjects were extensively tested before initiation of treatment and at intervals during the research. All but one of the side effects reported were mild, but some not previously reported were noted. All were monitored to resolution. Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of spinal cord injuries and an improved understanding of thresholds for side effects of 4-AP. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.
- 5. Independent Ethics Review:** The study reports that it was "initiated after its acceptance by both the local research committee of the hospital and the National Research Council of the IMSS." The Instituto Mexicano del Seguro Social (IMSS) has an IRB (#3566) registered with OHRP, and holds a Federal-Wide Assurance (#4956). No standard of ethical conduct is cited.
- 6. Informed Consent:** The study reports that patients were fully informed in writing and orally, and provided signed consent.

- 7. Respect for Potential and Enrolled Subjects:** The privacy of subjects was not compromised in the published report. Six exercised their freedom to decline to participate or to withdraw.

B. Compliance with Ethical Standard Prevailing when the Research Was Conducted

This research was conducted in 1999-2000 at the at the Spinal Cord Clinic of the Research Medical Unit for Neurological Diseases at the Specialties Hospital, Centro Médico Nacional Siglo XXI, of the Instituto Mexicano del Seguro Social in Mexico City. Because this institution holds a Federal-Wide Assurance from OHRP, the Common Rule is the applicable standard.

C. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, "Protections for Subjects in Human Research," effective on April 7, 2006. Section 26.1704 of that rule provides in pertinent part:

EPA shall not rely on data from any research initiated before [effective date of the final rule] if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

In addition, 40 CFR §26.1703 (as amended August 22, 2006) provides in pertinent part:

EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

I have applied these two standards in arriving at the conclusions below.

D. Conclusions

The ethical conduct of this study is documented more completely than is typical in published research. The Instituto Mexicano del Seguro Social in Mexico City has a registered IRB and holds a Federal-Wide Assurance from OHRP, and there is no indication that this research was not conducted in compliance with the applicable standards.

Subjects were all at least 18 years old. Pregnant females were excluded. Thus 40 CFR §26.1703 does not prohibit EPA reliance on this study.

In my judgment, there is no clear and convincing evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways, or that the ethical conduct of this study was significantly deficient relative to the standards prevailing when it was conducted. Therefore I see no barrier in EPA's regulations to consideration of and reliance on this study, assuming it is deemed to be scientifically valid.

Attachment

Summary Framework for Ethical Assessment

May 25, 2007

Grijalva, I., *et al.* (2003) Efficacy and Safety of 4-Aminopyridine in Patients With Long-Term Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Trial. *Pharmacotherapy* 23(7):823-834. MRID 47093601.

1. Value of Research to Society:

This report describes a randomized, placebo-controlled, double-blind crossover study in 27 non-pregnant adult out-patients with traumatic spinal cord injury of at least 1.5 years' duration. This paper reports improvements in the patients' condition with some side effects but no significant associated drug toxicity. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.

a. What was the stated purpose of the research?

To study the efficacy and safety of 4-Aminopyridine (4-AP) and to document sensorimotor changes after discontinuation of the drug in patients with long-term spinal cord injury.

b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?

Yes.

c. Does it test a hypothesis that can generate important knowledge about human biological systems?

No explicit hypothesis is stated.

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?

Results were published.

e. What government, organization, company and/or institution(s) funded the research?

The research was conducted at the Spinal Cord Clinic of the Research Medical Unit for Neurological Diseases at the Specialties Hospital, Centro Médico Nacional Siglo XXI, of the Instituto Mexicano del Seguro Social in Mexico City. It was funded by Instituto Mexicano del Seguro Social and Centro de Investigación y Estudios Avanzados, Instituto Politécnico Nacional.

2. Scientific Design:

I defer to others for a full review of the scientific validity and utility of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

a. Did the research have a clear scientific objective? Yes.

b. Was the research designed using accepted principles, methods, and reliable practices?

The design appears to reflect relevant prior research and accepted principles, methods, and practices.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?

This randomized, placebo-controlled, double-blind crossover study in 27 patients with long-standing SCI reports therapeutic effects of 4-AP administered orally for 12 weeks and lasting effects after discontinuation of 4-AP treatment, and summarizes side effects of treatment. All subjects started with placebo for two weeks. Half the subjects received 30 mg/day 4-AP orally for 12 weeks followed by placebo for 12 weeks; the other half received placebo for 12 weeks followed by 30 mg/day 4-AP for 12 weeks. Positive gains in motor function, sensation, and independence occurred more frequently in patients receiving 4-AP, and persisted after discontinuation of the drug. Fourteen (56%) patients had 26 adverse reactions—all but one of them mild, including dry mouth, dizziness, nausea, gastritis, and oral and peripheral paresthesia. One patient experienced posterior tibial artery vasospasm. Six patients (24%) experienced transitory changes in enzyme levels.

<p>d. Did the research design have sufficient power to definitively test the objective? I defer to others for this judgment.</p>
<p>e. To what purpose is the study used, or proposed for use, in the Agency? To characterize human threshold responses to 4-AP.</p>
<p>3. Subject Selection: 21 men and 4 non-pregnant women with traumatic spinal cord injuries of at least 1.5 years' duration completed the study. Two additional subjects (sex not reported) began the study but did not complete it; three more withdrew late in the study, but their results were included in the analysis. Age range of subjects was 23-48 years. The means by which subjects were recruited are not reported. Before enrolling, each participant underwent a comprehensive clinical evaluation. Exclusion criteria included pregnancy or lactation. There is no indication that subjects were recruited on any basis other than the scientific goals of the study.</p>
<p>a. Were subjects recruited and enrolled solely on the basis of the scientific goals of the study? Inclusion criteria included SCI of more than 1.5 years duration, age 18-60, and women who were postmenopausal, surgically sterile, or using acceptable methods of birth control. Before enrolling each participant underwent a comprehensive clinical evaluation. Exclusion criteria included pregnancy or lactation, any of a wide range of illnesses, allergy to pyridines, and various other factors. There is no indication that subjects were recruited on any basis other than the scientific goals of the study.</p>
<p>b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group? Apart from the fact that all subjects had a serious disability, no especially vulnerable groups were used in the study.</p>
<p>4. Risks and Benefits: Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. This research was undertaken to explore longer-term exposures to daily 4-AP and the potential for lasting effects after discontinuation of 4-AP treatment. Subjects were extensively tested before initiation of treatment and at intervals during the research. All but one of the side effects reported were mild, but some not previously reported were noted. All were monitored to resolution. Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of spinal cord injuries and an improved understanding of thresholds for side effects of 4-AP. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.</p>
<p>a. What were the risks to individual subjects? How were they minimized? Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. This research was undertaken to explore longer-term exposures to daily 4-AP. Subjects were extensively tested before initiation of treatment and at intervals during the research. All side effects were monitored to resolution.</p>
<p>b. If the research presents no direct benefits to individual subjects, what are the expected societal benefits from the study, and do they justify the incremental risk to individual subjects? The research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of spinal cord injuries and an improved understanding of thresholds for side effects of 4-AP. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.</p>
<p>c. What compensation was paid to the participants in the study? Not reported.</p>

5. Independent Ethics Review:

The study reports that it was “initiated after its acceptance by both the local research committee of the hospital and the National Research Council of the IMSS.” The Instituto Mexicano del Seguro Social (IMSS) has an IRB (#3566) registered with OHRP, and holds a Federal-Wide Assurance (#4956). No standard of ethical conduct is identified. Because the research was conducted by an institution holding a Federal-Wide Assurance from OHRP, the Common Rule is the applicable standard.

a. Was the research asserted to have been overseen by an ethics review body unaffiliated with the research?

The study reports that it was “initiated after its acceptance by both the local research committee of the hospital and the National Research Council of the IMSS.” The Instituto Mexicano del Seguro Social (IMSS) has an IRB (#3566) registered with OHRP, and holds a Federal-Wide Assurance (#4956).

b. Was the research asserted to comply with a standard of ethical conduct? What standard?

No standard of ethical conduct is identified. Because the research was conducted by an institution holding a Federal-Wide Assurance from OHRP, the Common Rule is the applicable standard.

6. Informed Consent:

The study reports that patients were fully informed in writing and orally, and provided signed consent.

a. Does the research assert that informed consent was obtained from all participants?

Yes.

b. How and under what circumstances was informed consent obtained?

“All patients were fully informed about the trial, all received a written description of the trial, and their questions and concerns were answered orally. All patients signed an informed consent letter.”

7. Respect for Potential and Enrolled Subjects:

The privacy of subjects was not compromised in the published report. Six exercised their freedom to decline to participate or to withdraw.

a. Was information about individual subjects managed so as to ensure their privacy?

No information about individual subjects was reported.

b. Were subjects free to withdraw from the research without penalty?

Two candidates declined to participate in the research; two more withdrew for reasons unrelated to the research; one was excluded due to a moderate adverse reaction; one more “dropped out” and another “did not attend the last evaluation.”



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MAY 25, 2007

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of 4-Aminopyridine Human Study

FROM: John M. Carley
Human Research Ethics Review Officer

TO: Ray Kent, Chief
Reregistration Branch 4, HED

REF: Segal, J., *et al.* (1999) Safety and Efficacy of 4-Aminopyridine in Humans with Spinal Cord Injury: A Long-Term, Controlled Trial. *Pharmacotherapy* 19(6):713-723, 1999. MRID 47093602.

This review characterizes the ethical conduct of the research reported in the referenced document in terms of the ethical standards which prevailed when the study was performed. The review applies a variant of the "Summary Framework for Ethical Assessment" developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached.

This study was conducted in the United States in the late 1990s, at the VA Medical Center in Long Beach, California. It was reported to have been approved by the U.S. FDA. The FDA rules at 21 CFR parts 50 and 56 and the Common Rule were the prevailing standards applicable to this research.

E. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the study under the seven headings used in the attached framework. Supporting details are in the attachment.

- 1. Value of Research to Society:** This report describes a randomized, active-treatment-controlled, partially-blinded study in 21 non-pregnant adult patients with traumatic spinal cord injury of at least two years duration. This paper reports improvements in the patients' condition with some minor side effects but no significant associated drug toxicity. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.
- 2. Scientific Design:** I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.
- 5. Subject Selection:** Subjects included 18 men and 3 women with traumatic spinal cord injuries of at least 2 years duration. One additional subject (sex not reported) began the study but did not complete it. Ten subjects had previously been exposed to 4-AP in a short-term test; the remaining 11 had never been exposed to 4-AP. Pregnant women were excluded. The means by which subjects were recruited are not reported. One additional subject started the study but moved out of the area and did not complete it. There is no indication that subjects were recruited on any basis other than the scientific goals of the study.
- 6. Risks and Benefits:** Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. This research was undertaken to explore longer-term exposures to daily 4-AP. Subjects were extensively tested before initiation of treatment and at intervals during the research. Although the study was conducted on an outpatient basis, investigators maintained daily telephone contact with subjects. All side effects were monitored to resolution. Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of spinal cord injuries and an improved understanding of thresholds for side effects of 4-AP. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.
- 8. Independent Ethics Review:** The study reports that all subjects "provided institution-approved, written informed consent." It states that it was "conducted with the approval of the U.S. Food and Drug Administration," but does not otherwise mention ethics oversight. The VA Long Beach Health Care System has an IRB (#214) registered with OHRP, and holds a Federal-Wide Assurance (#4435).
- 9. Informed Consent:** The study reports that informed consent was obtained from all patients. No further details are provided.

7. Respect for Potential and Enrolled Subjects: The privacy of subjects was not compromised in the published report.

F. Compliance with Ethical Standard Prevailing when the Research Was Conducted

This research was, in effect, a “Phase 2” drug trial, in which both therapeutic efficacy and objective and subjective side effects were closely monitored. It was conducted in the late 1990’s at the VA Long Beach Hospital with oversight from U.S. FDA, and although no specific standard of ethical conduct is cited, the Common Rule and the FDA rules at 21 CFR parts 50 and 56 prevailed and were applicable when the research was conducted. Although there are some gaps in documentation of ethical conduct, no noteworthy deficiencies relative to these standards were identified.

G. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, “Protections for Subjects in Human Research,” effective on April 7, 2006. Section 26.1704 of that rule provides in pertinent part:

EPA shall not rely on data from any research initiated before [effective date of the final rule] if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

In addition, 40 CFR §26.1703 (as amended August 22, 2006) provides in pertinent part:

EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

I have applied these two standards in arriving at the conclusions below.

H. Conclusions

The minor gaps in the documentation of the ethical conduct of this study, particularly with respect to details of the methods used to recruit, inform, and seek consent of subjects, are common in published research from this period. The VA Long Beach Medical System has a registered IRB and holds a Federal-Wide Assurance from

OHRP, and there is no indication that this research was not conducted in compliance with the applicable standards.

Subjects were all at least 18 years old. Pregnant females were excluded. Thus 40 CFR §26.1703 does not prohibit EPA reliance on this study.

In my judgment, there is no clear and convincing evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways, or that the ethical conduct of this study was significantly deficient relative to the standards prevailing when it was conducted. Therefore I see no barrier in EPA's regulations to consideration of and reliance on this study, assuming it is deemed to be scientifically valid.

Attachment

Summary Framework for Ethical Assessment

May 25, 2007

Segal, J., *et al.* (1999) Safety and Efficacy of 4-Aminopyridine in Humans with Spinal Cord Injury: A Long-Term, Controlled Trial. *Pharmacotherapy* 19(6):713-723, 1999. MRID 47093602.

1. Value of Research to Society:

This report describes a randomized, active-treatment-controlled, partially-blinded study in 21 non-pregnant adult patients with traumatic spinal cord injury of at least two years duration. This paper reports improvements in the patients' condition with some minor side effects but no significant associated drug toxicity. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.

a. What was the stated purpose of the research?

To determine the effects of the long-term administration of 4-aminopyridine (4-AP) on sensorimotor function in humans with long-standing spinal cord injury.

b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?

Yes. This study shows statistically significant increases in composite motor and sensory scores as well as other improvements in patients receiving oral 4-AP at 30 mg/day. Biochemical profiles and EEGs were unchanged from baseline, and no significant drug toxicity was encountered.

c. Does it test a hypothesis that can generate important knowledge about human biological systems?

No explicit hypothesis is stated.

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?

Results were published.

e. What government, organization, company and/or institution(s) funded the research?

The research was conducted at the Long Beach CA VA hospital. The source of funding was not reported. 4-AP was provided by Regis Technologies, Morton Grove IL.

2. Scientific Design:

I defer to others for a full review of the scientific validity and utility of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

a. Did the research have a clear scientific objective? Yes.

b. Was the research designed using accepted principles, methods, and reliable practices?

The design appears to reflect relevant prior research and accepted principles, methods, and practices.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?

This randomized, low-dose-active-treatment-controlled, partially-blinded study in 21 patients with long-standing SCI reports therapeutic effects of 4-AP administered orally for 3 months, and summarizes side effects of treatment. High-dose subjects received 30 mg/day 4-AP orally; the low-dose control group received 6 mg/day 4-AP. No clinically significant adverse effects or measurable toxicity was reported. Principal side effects observed included nervousness, giddiness or dizziness, and mild abdominal cramping or nausea. These side effects were transient, self-limited, or disappeared with changes in dosage or timing of drug treatment to coincide with meals. EEG, ECG, biochemical and hematological profiles, and urinalyses remained within normal range.

d. Did the research design have sufficient power to definitively test the objective?

I defer to others for this judgment.

e. To what purpose is the study used, or proposed for use, in the Agency?

To characterize human threshold responses to 4-AP.

3. Subject Selection:

Subjects included 18 men and 3 women with traumatic spinal cord injuries of at least 2 years duration. One additional subject (sex not reported) began the study but did not complete it. Ten subjects had previously been exposed to 4-AP in a short-term test; the remaining 11 had never been exposed to 4-AP. Pregnant women were excluded. The means by which subjects were recruited are not reported. One additional subject started the study but moved out of the area and did not complete it. There is no indication that subjects were recruited on any basis other than the scientific goals of the study.

a. Were subjects recruited and enrolled solely on the basis of the scientific goals of the study?

Inclusion criteria were SCI of more than 2 years duration. Subjects did not differ significantly in age, height, weight, or injury duration. All were non-pregnant adults. Before enrolling each participant underwent a comprehensive history and physical examination and detailed neurological examination. Exclusion criteria were epilepsy, seizures, abnormal EEG, recreational or illicit drug use, ethanol abuse, maintenance treatment with bronchodilators, use of anticholinergic or antihistaminic drugs, psychological disorders, and pregnancy or inadequate contraceptive measures. There is no indication that subjects were recruited on any basis other than the scientific goals of the study.

b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group?

Apart from the fact that all subjects had a serious disability, no especially vulnerable groups were used in the study.

4. Risks and Benefits:

Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. This research was undertaken to explore longer-term exposures to daily 4-AP. Subjects were extensively tested before initiation of treatment and at intervals during the research. Although the study was conducted on an outpatient basis, investigators maintained daily telephone contact with subjects. All side effects were monitored to resolution. Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of spinal cord injuries and an improved understanding of thresholds for side effects of 4-AP. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.

a. What were the risks to individual subjects? How were they minimized?

Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. This research was undertaken to explore longer-term exposures to daily 4-AP. Subjects were extensively tested before initiation of treatment and at intervals during the research. Although the study was conducted on an outpatient basis, investigators maintained daily telephone contact with subjects. All side effects were monitored to resolution.

b. If the research presents no direct benefits to individual subjects, what are the expected societal benefits from the study, and do they justify the incremental risk to individual subjects?

The research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of spinal cord injuries and an improved understanding of thresholds for side effects of 4-AP. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.

c. What compensation was paid to the participants in the study?

Not reported.

5. Independent Ethics Review:

The study reports that all subjects “provided institution-approved, written informed consent.” It states that it was “conducted with the approval of the U.S. Food and Drug Administration,” but does not otherwise mention ethics oversight. The VA Long Beach Health Care System has an IRB (#214) registered with OHRP, and holds a Federal-Wide Assurance (#4435).

a. Was the research asserted to have been overseen by an ethics review body unaffiliated with the research?

The study reports only that all subjects “provided institution-approved, written informed consent.” The VA Long Beach Health Care System has an IRB (#214) registered with OHRP, and holds a Federal-Wide Assurance (#4435).

b. Was the research asserted to comply with a standard of ethical conduct? What standard?

No standard of ethical conduct is identified. Because the research was conducted at VA Long Beach, and because of the citation of FDA approval, the Common Rule and 21 CFR 50 and 56 are the applicable standards.

6. Informed Consent:

The study reports that written informed consent was obtained from all patients. No further details are provided.

a. Does the research assert that informed consent was obtained from all participants?

All subjects “provided institution-approved, written informed consent.”

b. How and under what circumstances was informed consent obtained?

Not reported.

7. Respect for Potential and Enrolled Subjects:

The privacy of subjects was not compromised in the published report.

a. Was information about individual subjects managed so as to ensure their privacy?

No information about individual subjects was reported.

b. Were subjects free to withdraw from the research without penalty?

Not reported. One subject withdrew during the research because of moving out of the area.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MAY 22, 2007

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of 4-Aminopyridine Human Study

FROM: John M. Carley
Human Research Ethics Review Officer

TO: Ray Kent, Chief
Reregistration Branch 4, HED

REF: Van Diemen, H., et al. (1993) 4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety. *Clinical Neuropharmacology* vol. 16 No. 3, pp. 195-204. MRID 47093603.

This review characterizes the ethical conduct of the research reported in the referenced document in terms of the ethical standards which prevailed when the study was performed. The review applies a variant of the "Summary Framework for Ethical Assessment" developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached.

This study was conducted in the Netherlands in the early-1990s, at the Free University Hospital, Amsterdam. No standard of ethical conduct is identified in the report. I have assumed the 1989 Declaration of Helsinki to have prevailed when the research was conducted.

I. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the study under the seven headings used in the attached framework. Supporting details are in the attachment.

- 1. Value of Research to Society:** This report describes a randomized, placebo-controlled, double-blind, crossover study in 70 patients with MS, conducted at the Free University Hospital, Amsterdam. The source of financial support is not reported. The authors had previously reported a possible therapeutic effect of 4-aminopyridine (4-AP) on patients with MS; this paper reports the relationship between dosage, serum level, efficacy, and safety of 4-AP in the same patients. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.
- 2. Scientific Design:** I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.
- 7. Subject Selection:** Subjects included 43 women and 37 men with multiple sclerosis. Their ages ranged from 23 to 68; they had had MS for periods from 2 months to 25 years. Subjects had no hepatic or renal disease nor any history of epilepsy. Reproductive or nursing status of the women was not reported. The means by which subjects were recruited are not reported. All 70 subjects participated in the first phase of the research; one did not participate in the second phase for reasons unrelated to this study.
- 8. Risks and Benefits:** Earlier studies had reported serious side effects, such as a confusional state and epileptic fits, from clinical use of 4-AP to treat MS. This study employed a rising-dose design combined with close monitoring to explore the relationship between dosage, serum level, efficacy, and safety of 4-AP used to treat patients with MS. All subjective side effects were registered; as they increased, dosing was lowered or discontinued. All side effects were monitored to resolution. Blood chemistry was extensively monitored, as were cardiac, hepatic, and renal function. Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits are an improved understanding of thresholds for side effects of 4-AP, including pain, paresthesia, dizziness, headache, gait instability, nausea, restlessness/anxiety, abdominal pain, and obstipation. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.
- 5. Independent Ethics Review:** The study reports that the protocol was approved by the Ethical Committee of the Free University Hospital, Amsterdam. It does not identify any specific standard of ethical conduct.

10. Informed Consent: The study reports that informed consent was obtained from all patients before they were accepted into the study. No further details are provided.

7. Respect for Potential and Enrolled Subjects: The privacy of subjects was not compromised in the published report.

J. Compliance with Ethical Standard Prevailing when the Research Was Conducted

This research was, in effect, a “Phase 2” drug trial, in which both therapeutic efficacy and objective and subjective side effects were closely monitored. It was conducted in the early 1990’s, and although no specific standard of ethical conduct is cited, the Declaration of Helsinki, 1989, is assumed to have prevailed when the research was conducted. Although there are some gaps in documentation of ethical conduct, no noteworthy deficiencies relative to the standards of the Declaration of Helsinki were identified.

K. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, “Protections for Subjects in Human Research,” effective on April 7, 2006. Section 26.1704 of that rule provides in pertinent part:

EPA shall not rely on data from any research initiated before [effective date of the final rule] if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

In addition, 40 CFR §26.1703 (as amended August 22, 2006) provides in pertinent part:

EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

I have applied these two standards in arriving at the conclusions below.

L. Conclusions

The minor gaps in the documentation of the ethical conduct of this study, particularly with respect to details of the methods used to recruit, inform, and seek

consent of subjects, are common in published research from this period. All key requirements of the Declaration of Helsinki were addressed.

Subjects were all at least 18 years old. Roughly half the subjects were female, but the report is silent with respect to their reproductive or nursing status. There is no evidence to suggest that any were pregnant or nursing; in such cases it is EPA's policy that §26.1703 does not prohibit reliance on a study.

In my judgment, there is no clear and convincing evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways, or that the ethical conduct of this study was significantly deficient relative to the standard assumed to have prevailed when it was conducted. Therefore I see no barrier in EPA's regulations to consideration of and reliance on this study, assuming it is deemed to be scientifically valid.

Attachment

Summary Framework for Ethical Assessment

May 22, 2007

Van Diemen, H., et al. (1993) 4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety. *Clinical Neuropharmacology* vol. 16 No. 3, pp. 195-204. MRID 47093603.

1. Value of Research to Society:

This report describes a randomized, placebo-controlled, double-blind, crossover study in 70 patients with MS, conducted at the Free University Hospital, Amsterdam. The source of financial support is not reported. The authors had previously reported a possible therapeutic effect of 4-aminopyridine (4-AP) on patients with MS; this paper reports the relationship between dosage, serum level, efficacy, and safety of 4-AP in the same patients. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.

a. What was the stated purpose of the research?

To characterize the relationship between dosage, serum level, efficacy, and safety of 4-AP when used intravenously or orally to treat patients with Multiple Sclerosis.

b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?

Yes. Earlier studies had shown both beneficial effects of 4-AP and significant side effects. This study shows both beneficial effects and manageable side effects, especially with oral dosing.

c. Does it test a hypothesis that can generate important knowledge about human biological systems?

No explicit hypothesis is stated.

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?

Results were published.

e. What government, organization, company and/or institution(s) funded the research?

Not reported.

2. Scientific Design:

I defer to others for a full review of the scientific validity and utility of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

a. Did the research have a clear scientific objective? Yes.

b. Was the research designed using accepted principles, methods, and reliable practices?

The design appears to reflect relevant prior research and accepted principles, methods, and practices.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?

This report of a randomized, placebo-controlled, double-blind, crossover study in 70 patients with MS describes the relationship between dosage, serum level, efficacy, and safety of 4-AP administered intravenously (phase I) and orally (phase II) in a rising-dose protocol. Administered doses in phase I ranged from 0.07-0.5 mg/kg/bw; the duration of infusion ranged from 60 to 260 min. Principal side effects observed in phase I were pain or paresthesia; in 32 patients (46%) side effects were considered reasons to stop the infusion. All side effects gradually reversed within 2 h after discontinuing infusion. Seven patients (10%) showed no side effects in phase I. Administered doses in phase II ranged from 10-50 mg/day. In general, side effects in phase II were reported to be mild, and were less serious than those associated with intravenous administration. Nonetheless 14 patients (20%) needed dose reduction and three (4.4%) withdrew from the study because of these reported side effects. Most patients reported side effects within 30-45 min. after taking the medication; these effects generally resolved within 2-5 h. Fifteen patients (22%) showed no side effects in phase II. No effects were found on ECGs or on bone marrow, renal, cardiac or hepatic function.

<p>d. Did the research design have sufficient power to definitively test the objective? I defer to others for this judgment.</p>
<p>e. To what purpose is the study used, or proposed for use, in the Agency? To characterize human threshold responses to 4-AP.</p>
<p>3. Subject Selection: Subjects included 43 women and 37 men with multiple sclerosis. Their ages ranged from 23 to 68; they had had MS for from 2 months to 25 years. Subjects had no hepatic or renal disease nor any history of epilepsy. Reproductive or nursing status of the women was not reported. The means by which subjects were recruited are not reported. All 70 subjects participated in the first phase of the research; one did not participate in the second phase for reasons unrelated to this study.</p>
<p>a. Were subjects recruited and enrolled solely on the basis of the scientific goals of the study? There is no indication that subjects were recruited on any basis other than the scientific goals of the study.</p>
<p>b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group? Apart from the fact that all subjects had a serious disability, no especially vulnerable groups were used in the study.</p>
<p>4. Risks and Benefits: Earlier studies had reported serious side effects, such as a confusional state and epileptic fits, from clinical use of 4-AP to treat MS. This study employed a rising-dose design combined with close monitoring to explore the relationship between dosage, serum level, efficacy, and safety of 4-AP used to treat patients with MS. All subjective side effects were registered; as they increased, dosing was lowered or discontinued. All side effects were monitored to resolution. Blood chemistry was extensively monitored, as were cardiac, hepatic, and renal function. Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits are an improved understanding of thresholds for side effects of 4-AP, including pain, paresthesia, dizziness, headache, gait instability, nausea, restlessness/anxiety, abdominal pain, and obstipation. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.</p>
<p>a. What were the risks to individual subjects? How were they minimized? Earlier studies had reported serious side effects, such as a confusional state and epileptic fits, from clinical use of 4-AP to treat MS. This study employed a rising-dose design combined with close monitoring to explore the relationship between dosage, serum level, efficacy, and safety of 4-AP used to treat patients with MS. All subjective side effects were registered; as they increased, dosing was lowered or discontinued. All side effects were monitored to resolution. Blood chemistry was extensively monitored, as were cardiac, hepatic, and renal function.</p>
<p>b. If the research presents no direct benefits to individual subjects, what are the expected societal benefits from the study, and do they justify the incremental risk to individual subjects? The research offered therapeutic benefits to subjects. Societal benefits include an improved understanding of thresholds for side effects of 4-AP, including pain, paresthesia, dizziness, headache, gait instability, nausea, restlessness/anxiety, abdominal pain, and obstipation. Information provided suggests that these benefits were sufficient to justify the risks to individual subjects.</p>
<p>c. What compensation was paid to the participants in the study? Not reported.</p>
<p>5. Independent Ethics Review: The study reports that the protocol was approved by the Ethical Committee of the Free University Hospital, Amsterdam. It does not identify any specific standard of ethical conduct; the Declaration of Helsinki (1989) is assumed to have applied.</p>

<p>a. Was the research asserted to have been overseen by an ethics review body unaffiliated with the research? The protocol was approved by the Ethical Committee of the Free University Hospital, Amsterdam.</p>
<p>b. Was the research asserted to comply with a standard of ethical conduct? What standard? No standard of ethical conduct is identified. The Declaration of Helsinki (1989) is assumed to have applied.</p>
<p>6. Informed Consent: The study reports that informed consent was obtained from all patients before they were accepted into the study. No further details are provided.</p>
<p>a. Does the research assert that informed consent was obtained from all participants? Informed consent was obtained from all patients before they were accepted into the study.</p>
<p>b. How and under what circumstances was informed consent obtained? Not reported.</p>
<p>7. Respect for Potential and Enrolled Subjects: The privacy of subjects was not compromised in the published report.</p>
<p>a. Was information about individual subjects managed so as to ensure their privacy? No information about individual subjects was reported.</p>
<p>b. Were subjects free to withdraw from the research without penalty? Not reported. One subject withdrew between phases I and II of the research for reasons reported to be unrelated to the study.</p>