ORISE
OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION

November 09, 2007

Radiogardase®-Cs
Insoluble Prussian Blue (ferric hexacyanoferrate, $Fe_4[Fe(CN)_6]_3$)

INFORMATIONAL MATERIAL

PACKAGE INSERT*

DESCRIPTION

IND 51,700, insoluble Prussian Blue, is to be used in the U.S. as a decorporation agent for patients internally contaminated with medically significant amounts of cesium and thallium. In this document, the name Insoluble Prussian Blue (PB) without further specification indicates the following compound:[1]

Ferric(III) hexacyanoferrate(II) "insoluble PB"
Fe_4 [Fe $(CN)_6]_3$
Molecular weight: 859.3
Color Index No. 77.510
CAS Registry No. 14038-43-8

Prussian Blue is distributed by Oak Ridge Institute for Science and Education (ORISE). ORISE is managed by Oak Ridge Associated Universities (ORAU), under contract with the U.S. Department of Energy (DOE), Contract No. DE-AC05-76OR00033. A selected bibliography of the world use of Prussian Blue in cesium and thallium decorporation therapy is given in the accompanying references.

INTRODUCTION

Insoluble Prussian Blue (PB), ferric hexacyanoferrate, $Fe_4[Fe(CN)_6]_3$ is a drug that enhances excretion of isotopes of cesium and thallium from the body by means of ion exchange. It has had a long and successful history in the treatment of internal contamination with radiocesium. Prussian Blue is currently only supplied by a German company, HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG (HEYL GmbH), under the trade name Radiogardase[7]. The Oak Ridge Institute for Science and Education (ORISE) undertaking for this IND will: (1) make Insoluble Prussian Blue more widely available at Department of Energy (DOE) facilities for physicians to treat individuals with significant radiocesium and radiothallium contamination and (2) quantitate efficacy and establish a drug profile based on wider experience. In the DOE system, internal contamination with radiocesium is expected to be much more important than with thallium. This protocol will therefore deal primarily with decorporation therapy with PB for internal contamination with radiocesium.

Of the various radioisotopes of cesium, ^{137}Cs is the most important. ^{137}Cs is a common fission by-product material, a frequent active component of sealed sources, and an important radionuclide in radiation oncology. The use of ^{137}Cs falls under the jurisdiction of the Nuclear Regulatory Commission (NRC). It is a ubiquitous radionuclide found throughout the DOE system and in hospitals performing either gynecological brachytherapy or interstitial therapy for solid tumors. Until the Goiânia incident in Brazil,[2] there were very few cases of radiocesium contamination requiring decorporation therapy. However, there is an increasing potential for such contamination to occur and a need for specific therapy. The recent increase in workers performing remediation work at hazardous waste sites also requires that clinicians have Insoluble Prussian Blue available and understand the nature of its pharmacodynamics.

Insoluble Prussian Blue has been recommended for years as the drug of choice by national and international radiation protection societies for use in treating internal contamination with radiocesium. It was effectively used in the treatment of patients contaminated with ^{137}Cs in the 1987 Goiânia, Brazil accident under temporary clearance by FDA for "compassionate use" by the Oak Ridge Associated Universities' Radiation Emergency Assistance Center/Training Site (REAC/TS) program. The majority of the Prussian Blue used for treatment in the Goiânia, Brazil accident was supplied by HEYL GmbH.

***Reviewed and approved by the Oak Ridge Site Wide Institutional Review Board for 12 months, November 09, 2007.**

CLINICAL PHARMACOLOGY

Insoluble Prussian Blue has a very high affinity for cesium and thallium, whose metabolism follows an entero-enteric cycle. These ions are ordinarily excreted into the intestine and reabsorbed from the gut into the bile, and then excreted again into the GI tract. Orally administered PB traps thallium or cesium in the gut, interrupts its re-absorption from the gastrointestinal tract and thereby increases fecal excretion. Thus, the biological half-life of thallium and cesium is significantly reduced after decorporation therapy with PB. PB itself is not absorbed across the gut wall in significant amounts.

The mechanism of cesium and thallium adsorption by hexacyanoferrates is not yet known in full detail. All authors discuss chemical ion-exchange as a mode of action, in which nonstoichiometric and stoichiometric cations of the drug are exchanged by thallium or cesium ions.[3] Physical adsorption on the large molecular surface, possibly interacting with water, may also be involved. This phenomenon would explain the influence of the drying procedure on the efficacy of the drug.

Inversion of the concentration gradient of toxic metals between the central compartment and target organs occurs commonly in decorporation therapy with chelating agents, but this has not been seen with PB. The effect of PB in experimental thallium and cesium poisoning has been investigated in various animal studies that are outlined below in detail.

Cesium

In-vitro studies have shown that cesium readily binds to PB and the cesium absorption capacity of various hexacyanoferrates does not differ significantly. Administration of a single dose of radiocesium and the concomitant oral application of PB results in reduction of cesium uptake from the gastrointestinal tract. In piglets, PB reduced ^{137}Cs uptake by more than 97%. Diminution of a ^{137}Cs-body-burden also depends on the dose of administered hexacyanoferrate (II) and if given as late as 60 minutes after ^{137}Cs administration, the enteral ^{137}Cs absorption is also suppressed. Autoradiography of rats administered labeled PB shows that the radioactivity is limited to the gastrointestinal tract.[4] In addition, chronic feeding of rats and piglets with ^{137}Cs-contaminated food and concomitant administration of PB resulted in reduced whole-body retention of ^{137}Cs.[5] In rats the effect on the whole-body retention was age-dependent. In younger animals, whole body retention was noted to be lower than in older animals, primarily due to a higher basal metabolic rate. In most cases where PB was given, the administered ^{137}Cs was found to be excreted primarily in the feces. In a mixture with other substances occasionally used in radiation medicine (for example Ca-alginate, potassium iodide), PB also decreased absorption of cesium into the organism and reduced the whole-body retention.[6]

Insoluble Prussian Blue increases the cumulative excretion of incorporated radiocesium in feces whereas in untreated animals most cesium is excreted in the urine. In animals treated with PB, fecal excretion predominates, resulting in a decreased biological half-life. In rats, decorporation therapy with PB resulted in the effective biological half-life diminished by 50% (–11 days vs. –6 days) and in dogs from 11 to 6.5 days.[7] These animal results parallel the human kinetic data noted in the radiological accident in Goiânia.

Thallium

The efficacy of PB for treatment of thallium poisoning has been described in various case reports.[8-10] In patients even with severe thallium poisoning, most cases published in the literature have had a favorable outcome. Only three deaths have been reported.[11,12] Two of these individuals ingested 2400 mg and 4000 mg of thallium, respectively (lethal dose approximately 1000 mg). One died after a second ingestion of thallium. However, the majority of patients with thallotoxicosis exhibit a good clinical response.

In the more severe cases of thallium intoxication, additional treatment for enhanced elimination is used. If ingestion had occurred within the preceding 48 hours, gastric lavage has been carried out in many cases. Hemodialysis and forced diuresis have also been used in many cases and hemoperfusion has been carried out in very severe cases. To increase the fecal excretion, laxatives (mannitol) were used and occasionally forced diarrhea was induced. The pharmacology of PB with regard to thallium poisoning is expected to be similar to that for cesium.

Therapy of thallium poisoning, similar to that for cesium, is primarily directed to prevention of absorption from the intestinal tract, interruption of enteric cycling, and elimination of the metal complexes from the body. In cases of severe thallium intoxication, additional types of elimination treatment may be necessary, such as:

- Induced emesis, followed by gastric intubation and lavage.
- Forced diuresis (8-12 1/24h) until urinary thallium excretion is less than 1 mg/24h.
- Charcoal hemoperfusion, which has been proven successful if used within 48 hours of thallium ingestion and, therefore, during the distribution phase.
- Hemodialysis has also been reported to be effective in thallium intoxication.

A survey of the literature[10] shows that forced diuresis and hemoperfusion with activated charcoal increases the total clearance of thallium and decreases its biological half-life, $t_{1/2}$,as follows:

- without treatment : $t_{1/2}$ 9.5 to 15 days
- PB only : $t_{1/2}$ 3.0 ∀ 0.7 days
- PB+forced diuresis : $t_{1/2}$ 2.0 ∀ 0.3 days
- PB+forced diuresis+hemoperfusion : $t_{1/2}$ 1.4 ∀ 0.3 days

PHARMACOKINETICS

PB is a non-resorbable compound acting only in the gastrointestinal tract. To study the degree of resorption of PB from the gastrointestinal tract, ^{39}Fe-labeled PB was administered to piglets.[13] Low amounts of iron were absorbed from PB. The whole-body retention was measured after 14 days (% of applied doses):

K ^{39}Fe [Fe(CN)$_6$] 1.47%	^{39}Fe$_4$ [Fe(CN)$_6$]$_3$ 1.34%
KFe [^{39}Fe (CN)$_6$] 0.2%	Fe$_4$[^{39}Fe(CN)$_6$]$_3$ 0.15%

Nearly all of the applied dose was found in the feces. Application of KFe [^{39}Fe(CN)$_6$] to rats resulted in 0.03% whole body retention (only in the gastrointestinal tract) and in traces of radioactivity in the urine (0.14%). The amount in blood and skeleton was below the detection limit. Ninety-nine percent of the applied dose was excreted in feces. After administration of K^{39} Fe [Fe(CN)$_6$] to rats, traces of radioactivity were found in the skeleton (0.11%) and in the blood (0.046%). The differences in distribution of KFe[^{39}Fe(CN)$_6$] and K^{39} Fe [Fe(CN)$_6$] showed, that no PB is absorbed, but the different ions K^+, Fe^{3+} and [Fe(CN)$_6$]$^{4-}$ are metabolized instead. No evidence was obtained for decomposition of [Fe(CN)$_6$]$^{4-}$. Further studies on the decomposition of PB, especially with respect to the release of cyanide, are outlined in the toxicology section. Histopathological examination of different organs showed no deposits of PB after oral administration of insoluble PB.[14]

After intraperitoneal (IP) administration of KFe[^{39}Fe(CN)$_6$] the substance is eliminated by the reticuloendothelial system. The first day 40.5% of the radioactivity was excreted by urine; the fecal content was very small. On the second day 42% was found in the feces, and only a trace in the urine. After 4 days the body retention was 4.5%, with the most retention in the liver. Intravenous (IV) application of KFe[^{39}Fe(CN)$_6$] and K^{59}Fe[Fe(CN)$_6$] resulted in an entirely different metabolic behavior in rats. From K^{59}Fe[Fe(CN)$_6$] more than 50% of the radioactivity was excreted in the urine, but from KFe[^{39}Fe(CN)$_6$] only 0.06% was excreted. The fecal excretion was low for both. The distribution of the radioactivity into the organs after application of KFe(^{39}Fe(CN)$_6$] was similar to that after application of K$_4$[^{39}Fe(CN)$_6$] and differed from K^{59}Fe[Fe(CN)$_6$]. Whereas the radioactivity of K^{59}Fe[Fe(CN)$_6$] persisted in the liver for 8 days, the activity of K^{59}Fe[Fe(CN)$_6$] varied from the liver to the blood.

TOXICITY

The LD_{50} has been shown to be 1.13 mg/g after I.P. administration of ferric(III) hexacyanoferrate(II) to rats[4]. No tissue response could be detected. For oral application, the LD_{50} is >10 g/kg. Results of skin tolerance testing and eye testing in rabbits were negative.

PB contains cyanide ions bound to iron. At extremely low pH in the absence of oxidizing agents, PB decomposes and, under these circumstances, cyanide can be released. Since oral administration of PB is indicated in the treatment of thallium poisoning and cesium incorporation, the possibility of cyanide release must be excluded. Cyanide labeled with ^{14}C was incorporated into PB and used to study the possibility of cyanide release after PB administration.

1. KFe[Fe(CN)$_6$] 6 $K^+ + Fe^{3+} + [Fe(CN)_6]^{4-}$
   Fe$_4$[Fe(CN)$_6$]$_3$ 6 $4\ Fe^{3+} + 3\ [Fe(CN)_6]^{4-}$
2. [Fe(CN)$_6$]$^{4-}$ 6 $Fe^{2+} + 6\ CN^-$
3. CN^- 6 $\xrightarrow[\text{metabolism}]{}$ $CO_2 + SCN^-$

In-vitro, the release of cyanide is negligible.[15] Piglets were also administered ^{14}C-labeled ferric(III) hexacyanoferrate(II). No labeled $^{14}CO_2$ was detected in the expired air, thereby demonstrating that no significant amount of cyanide ions was released from PB in the body. The amount of incorporated cyanide ions is apparently extremely small or nil.

When PB was applied orally to rats for 12 weeks, no significant changes in increased body weight were found. Histopathological changes were not detectable in the organs including the gut. For chronic administration of PB to rats, the LD_{50} is > 1 g/kg.

Oral application of PB in food containing 1% PB over 120 days or over 60 days resulted in no change of body weight. Food consumption and body weight increase was unchanged during 10 days or 4 weeks. No significant difference of average fluid intake of

rats was detected in rats during a 60-day period. The well-being and body weight of dogs in no way was affected by PB during 11 days. At autopsy no pathological changes were observed.

PREVIOUS HUMAN EXPERIENCE

Thallium

Most of the patients who were treated immediately after Tl-ingestion with PB and other therapeutic regimens developed no, or only minimal traces of thallium-induced neurological symptoms, although the thallium levels were high. Some patients in whom start of treatment was delayed also recovered uneventfully. However, recovery progressed slowly sometimes. In some patients with severe clinical signs of thallium intoxication, clinical symptoms were not fully reversible at the time of discharge. Neurological disturbances, namely in the legs, and alopecia constituted most of the remaining clinical symptoms.

Cesium

The effect of PB on Cs decorporation initially was investigated in volunteer studies. A dosing schedule of Insoluble Prussian Blue of 1g tid was shown to reduce the effective biological half life of cesium to one-third of its usual value.[7,16] The administration of 0.5 g tid , (before and concomitantly given with) ^{137}Cs had no prophylactic effect on body burden. Patients tolerated Insoluble Prussian Blue without adverse effects except for slight obstipation. When PB was administered in a daily dose of 2 g divided in 10 single doses for 10 days, the biological half-life of ^{137}Cs was reduced from 115 to about 40 days.

In four of six volunteers, PB was found to block almost completely Cs uptake from contaminated food. However, the preexisting Cs body burden was not substantially decreased. The effect of PB varied individually, but did not appear to be dose-dependent. No adverse effects were observed.

The PB treatment of 46 patients with incorporated ^{137}Cs after the radiological accident in Goiânia, Brazil in 1987, when 249 persons had been contaminated externally or internally with ^{137}Cs, is described in the IAEA Report. Patients' ages 4 to 38 years were treated with Radiogardase®-Cs up to 150 days. Doses generally ranged from 1 to 10 g daily. In four adult cases, 20 g was administered daily in divided doses. Children were given 1-1.5 g daily in 2-3 divided doses. Insoluble Prussian Blue was found to significantly expedite cesium decorporation in these cases. Increasing the dose of PB generally resulted in higher radioactivity in the fecal samples while the systemic burden was reduced. In a few patients, constipation was observed that could be treated easily using laxatives.

In another incident, five persons had accidental intake of ^{137}Cs. The effective half-life of the cesium depended on the individual and ranged from 36 to 124 days. The half-life was shorter when the subject's weight was lower or the person was younger. PB accelerated the decorporation of cesium reducing the average effective half-life from 39 to 16 days.

In the 1987 Goiânia, Brazil ^{137}Cs contamination accident, an upper therapeutic range of Insoluble Prussian Blue was tentatively established at approximately 10 g orally per day in three divided doses. Doses higher than 10 g per day resulted in an increased incidence of gastritis, constipation and diarrhea. At six months' follow up, some patients still complained of gastrointestinal symptoms and one eventually developed a duodenal ulcer. Most of these adverse effects were mitigated significantly with dietary modification and with laxatives. It is also not certain whether these symptoms were due to other concomitant stressors, Insoluble Prussian Blue therapy, or other therapy. Several reviews of the scientific literature on use of PB in radiation accidents have recently been published.[18-24]

WARNINGS AND PRECAUTIONS

Insoluble Prussian Blue is effective only if gastrointestinal motility is intact. When insoluble Prussian Blue is given with tetracycline, it may retard the absorption of the tetracycline. There are no known absolute contraindications to the usage of PB, when medically indicated for decorporation therapy.

Usage in Pregnancy - Pregnancy Category C -

Insoluble Prussian Blue has been studied in pregnant rats with experimental thallium poisoning. The Tl-content of the placenta, brain, and liver of fetuses was noted to be reduced by PB, and the survival rate of the pregnant rats was increased. Oral administration of insoluble PB also was found to shorten the residence time of ^{137}Cs in pregnant, and lactating rats. The deposition of ^{137}Cs in the embryos of nursing young animals was similarly reduced. The efficacy of therapy with PB has been shown to be time-dependent. Start of treatment immediately after ingestion is most successful. As PB is not absorbed from the GI tract, teratogenic effects or appearance in milk are not to be expected. Pregnant and lactating women are therefore not excluded from treatment with PB.

ADVERSE REACTIONS

High doses during treatment over a prolonged period may lead to slight obstipation.

OVERDOSAGE

Overdosage by PB has not been described.

DOSAGE AND ADMINISTRATION

Insoluble Prussian Blue is administered orally. Depending on the severity of thallium poisoning or cesium incorporation, PB may be given from 3 g to 20 g, daily in three divided doses. Typically, for decorporation therapy for internally deposited radiocesium, the initial dosage is one gram three times daily and the dosage may be increased for more severe cases. The higher dose regimen (> 10 g daily) usually is preferred in acute poisoning with thallium. In cases of acute thallium poisoning in which thallium is still present in the stomach or the upper part of the small intestine, an initial dose of at least 3 g should be given at once.

The capsules of Radiogardase® -Cs are to be swallowed whole with some liquid or dispersed in warm water and drunk as a solution; the solution may also be administered via stomach tube following gastric lavage. If clinical findings suggest that oral ingestion is impossible, administration of PB is recommended by way of a duodenal tube. The duration of treatment depends on thallium or cesium identification in the stool by laboratory analysis.

HOW SUPPLIED

Insoluble Prussian Blue is supplied from HEYL GmbH in Germany as a 0.5 gram gelatin capsule for oral administration.

The Food and Drug Administration (FDA) requires that the Sponsor and Manager(s) of the IND be in a position to account for all ampules sent to investigator physicians. These physicians must, therefore, set up an accounting system on the supplies of Prussian Blue and be prepared to report their clinical experience annually, including observations on the safety and efficacy of the drug. The Manager(s) of the Prussian Blue IND will contact all co-investigators in June of each year to obtain this report. These observations will be incorporated into ORISE's summary report to the FDA for the preceding 12-month period.

SUMMARY OF ADMINISTRATION

To maximize efficacy, if the patient contaminated with ^{137}cesium or thallium also has been injured, assure that medical treatment is initiated as soon as possible. However, delay does not preclude the use of Prussian Blue (PB). The patient's respiratory/hemodynamic status should also be stable prior to administration of the drug. Since this application is directed to use of PB in the DOE facilities complex, the following guidelines pertain primarily to radiocesium since that isotope is expected, by far, to be the more commonly encountered isotope. The following guidelines are provided to facilitate rapid initiation of treatment.

<u>Therapy Guidelines</u>

1. The internal burden of radiocesium should be ascertained after an accidental ingestion or inhalation by appropriate whole-body counting and/or by bioassay:

(A) Determine the magnitude of the radiocesium accident. The appropriate annual limit of intake (ALI) should be determined with health physics assistance from 10 CFR20. For ^{137}Cs, this corresponds to 100 µCi for ingestion (3.7 E06 Bq) or 200 µCi (7.4 E06 Bq) for inhalation. For other radioisotopes of Cesium, the appropriate ALI should be determined.

(B) An estimate of the magnitude of the accident may be determined by whole body counting, early stool or urine sampling, or by gastric lavage. Accidents in the DOE facilities complex are expected generally to involve either ^{137}Cs particulate inhalation or ^{137}Cs in a contaminated wound. In these cases, whole body counting or wound counting would be the preferred mode for initial determination of the magnitude of the accident.

(C) After an initial whole body or wound count, the treating physician should propose a Prussian-Blue regimen based on the estimated body burden of ^{137}Cs.

(D) The level of internal contamination should be categorized (e.g. low, intermediate, high). For initial treatment guidelines, we consider a low-level accident as 1-5 ALI, a moderate accident as 5-10 ALI, and a severe accident as greater than or equal to 10 ALI.

(E) The appropriate daily dose of Prussian Blue should be based on the suspected level of internal contamination (e.g. low: 3 g daily; intermediate: 3-10 gm daily; high:10-20 g daily). All administration should be TID.

2. **In most cases requiring decorporation therapy, the extent of internal contamination is expected to be low to moderate (< 1-10 annual limits of intake, ALI). Prussian Blue decorporation therapy for radiocesium in these cases should be initiated at an initial dosage of one gram TID and titrated as necessary. In order to judge the efficacy of treatment, the patient should be followed periodically with both urine and fecal bioassay and with whole-body counting. In more serious cases of internal contamination with radiocesium, up to 10 grams or more of PB may be given daily in three divided doses. The patient should be warned that he/she may experience blue colored stool.**

3. **It is expected in cases involving decorporation therapy that daily whole body counting and collection of 24-hour urine and fecal bioassay samples will be performed. This will allow proper evaluation of ^{137}Cs elimination curves.**

4. **Since PB can also bind Na and K ions with lesser affinity than for Cs, those patients with potential for electrolyte abnormalities and/or cardiac problems should have periodic serum electrolyte evaluations at the discretion of the treating physician. Blood samples should also be collected every 12 hours for the first 96 hours post-accident for serum chemistry, especially, iron, ferritin, and serum electrolytes as indicated. A CBC should be collected initially and as indicated clinically thereafter. Vital signs should also be included in a timetable.**

5. **The attending physician should consider reducing the dose of Prussian Blue in parallel with the decreasing whole body burden of ^{137}Cs. A case report form (CRF) has been developed and co-investigators are expected to record cesium body burden and bioassay results at defined time intervals. It is also imperative that a description of measurement methods be included to facilitate analysis of data.**

6. **Hemodialysis and other extracorporeal clearance techniques have recently been proposed to aid elimination of radiocesium and such techniques could be considered for adjunctive therapy in severe cases of internal contamination.[25-26] In very severe cases involving internal contamination with radiocesium, the guidelines for thallium poisoning could also be employed.**

7. **Therapy for thallium poisoning is similar to that for cesium, except that an initial loading dose of 3 gm orally should be used. In cases of severe thallium intoxication, additional types of elimination treatment may be necessary, such as:**

    - **Induced emesis, followed by gastric intubation and lavage.**
    - **Forced diuresis (8-12 1/24h) until urinary thallium excretion is less than 1 mg/24h.**
    - **Charcoal hemoperfusion, which has been proven successful if used within 48 hours of thallium ingestion and, therefore, during the distribution phase.**
    - **Hemodialysis has also been reported to be effective in thallium intoxication.**

In more severe cases of thallium poisoning, up to 20 grams of PB may be given daily in three divided doses, depending on the severity of the patient's condition.

Questions regarding the use of Prussian Blue may be referred to one of the following co-principal investigators at the Oak Ridge Associated Universities, P. O. Box 117, Oak Ridge, TN 37831-0117:

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