DATA EVALUATION RECORD

8/15/2000

NTBC 9 (A Mesotrione Analogue)

Study Type: §Non-guideline; Pharmacokinetic Study of Two Formulations of the Mesotrione Analogue NTBC (SC0735) in Healthy Human Volunteers. Report of the Analytical Portion of the Study

Work Assignment No. 2-01-52NN (MRID 44505115)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer Guy Beretich, Ph.D.	Signature: _____ Date: 8/15/00
Secondary Reviewer Kelley Van Vreede, Ph.D.	Signature: _____ Date: 8/15/00
Program Manager Mary Menetrez, Ph.D.	Signature: _____ Date: 8/14/00
Quality Assurance Steven Brecher, Ph.D.	Signature: _____ Date: 8/15/00

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This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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EPA Reviewer: Joycelyn E. Stewart, Ph.D.
Science Analysis Branch/HED (7509C)

Work Assignment Manager: Marion Copley, DVM, DABT
Toxicology Branch 1/HED (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Single Dose Study - Man
OPPTS Number: None

OPP Guideline Number: §non-guideline

DP BARCODE: D259369
P.C. CODE: 122990

SUBMISSION CODE: S541375
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): NBTC (Not reported)

SYNONYMS: (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione); SC0735

CITATIONS: Stevens, V. (1998) A Single Dose, Crossover, Pharmacokinetic Study of Two Formulations of NTBC (SC0735) in Healthy Volunteers. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report No.: CTL/R/1360; /Study No.: CCT96/001, January 9, 1998. MRID 44505115. Unpublished.

SPONSOR: Zeneca Ag Products, Wilmington, DE

EXECUTIVE SUMMARY: In a special study (MRID 44505115), 10 healthy human male subjects were given a single oral dose of NTBC (purity not reported) at 1 mg/kg in either liquid or capsule (Period 1). After approximately 14 days, patients who received the liquid dose were dosed by capsule and vice versa (Period 2). Plasma tyrosine concentrations were determined from 0–120 hours post-dosing for both periods.

The purpose of the study was to compare the bioavailability of NTBC at therapeutic levels in two different formulations. This report constitutes the analytical portion of the study. The clinical portin of the study was performed at Cardiff Clinical Trials Ltd, Cardiff Medicentre, Heath Park, Cardiff, UK.

A single dose of NTBC increased mean plasma tyrosine levels in a linear fashion until approximately 48 hours after dosing, at which time tyrosine levels plateaued. At maximum levels, plasma tyrosine was 1039.6 nmol/mL. This level was increased 935% from a mean pretreatment level of 100.4 nmol/mL. After 14 days recovery, mean plasma tyrosine concentrations had not returned to pre-dosing levels and were still high (808.4 nmol/mL). Administration of the second dose of NTBC increased plasma tyrosine levels to a mean

maximum level of 1050.3 nmol/mL. This level is approximately equal to the maximum reached after the first dose, and is 946% greater than the first pre-dose measurement.

Dosing formulation appeared to not have an effect on the bioavailability of NTBC.

This is study is classified **acceptable (non-guideline)** and does satisfy the purposes for which it was intended.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Quality Assurance, and Flagging statements were provided.

I. MATERIALS AND METHODS

This section in the report presents only summary information on the performance of the study and is not a sufficient report thereof.

A. MATERIALS

1. Test material: NTBC, a triketone analogue of mesotrione
2. Vehicle: Capsule or liquid; composition of both was unspecified
3. Test subjects: Human male volunteers
4. Testing facility: Cardiff Clinical Trials Ltd, Cardiff Medicentre, Heath Park, Cardiff, UK

B. STUDY DESIGN

1. Purpose: Type I tyrosinemia is an hereditary deficiency of the enzyme fumarylacetoacetate hydrolase. This condition leads to a build up of fumarylacetoacetate (FAA) and maleylacetoacetate (MAA); these compounds and their decarboxylated products are known to be hepatotoxic and nephrotoxic. The incidence of hereditary tyrosinemia type I is relatively high in some areas of the world and life expectancy varies from 1 year to about 20 years. Previously the only effective treatment was liver transplantation; however, Lindstedt et al (1992) used NTBC (SC0735), a triketone, to block the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) and divert excess tyrosine to urine as phenolic acids. This action stopped the flow of substrate to the defective enzyme, preventing build up of the potentially lethal compounds. Lindstedt found that tyrosine levels were not elevated above approximately 800 nmol/mL and ocular lesions were not observed in patients treated with NTBC; however, many clinicians also chose to reduce the dietary intake of tyrosine in these patients.

   The purpose of this study was to compare the bioavailability of NTBC, at dose levels used in the clinic, from two different formulations in healthy volunteers.

2. Dosing preparation and administration - Dosing preparations were not specified. Ten healthy males were given a single dose (1mg/kg) of NTBC in either liquid or capsule (Period 1). After approximately 14 days, patients who received the liquid dose were dosed by capsule and vice versa (Period 2).

3. Statistics - No statistical analyses were employed. Data were summarized as means ± standard deviation and presented graphically.

C. METHODS:

1. Observations - No information provided.

2. Blood - Blood (plasma samples) were taken from all volunteers at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hours. All plasma samples were analyzed for tyrosine by reverse-phase HPLC and UV detection.

3. Urine - Urine samples were collected at 0-12, 12-24, 24-48, 48-72 and 72-96 hours from all volunteers, but were not reported to have been analyzed.

II. RESULTS

A single dose of NTBC increased mean plasma tyrosine levels in a linear fashion through approximately 48 hours after dosing, at which time tyrosine levels plateaued. At maximum levels, plasma tyrosine was 1039.6 nmol/mL. This level was increased 935% from a mean pretreatment level of 100.4 nmol/mL. After 14 days recovery, mean plasma tyrosine concentrations had not returned to pre-dosing levels and were still high (808.4 nmol/mL). Administration of the second dose of NTBC increased plasma tyrosine levels to a mean maximum level of 1050.3 nmol/mL. This level is approximately equal to the maximum reached after the first dose, and is 946% greater than the first pre-dose measurement. The mean plasma levels are reported in Table 1 and are plotted in Figure 1.

Table 1. Mean plasma tyrosine levels (nmol/mL) in human subjects receiving a single 1 mg/kg oral dose of NTBC at 0 (period 1) and 14 days (period 2).[a]

	Treatment Period	
Study hour	1	2
Pre-dose	100.4	808.4
0.25	86.2	443.8
0.5	128.6	547.1
0.75	118.3	714.0
1	115.0	532.4
1.5	110.7	752.4
2	121.6	725.6
2.5	116.5	710.3
3	128.2	756.0
3.5	133.6	710.5
4	135.5	735.5
6	236.8	766.9
8	303.4	783.5
10	319.8	787.1
12	382.8	635.0
24	562.3	729.0
48	795.5	1050.3
72	992.5	1002.2
96	994.8	1018.5
120	1039.6	1048.9

a Data are the mean of 3-10 subjects at each sampling interval and were calculated by the reviewers from data obtained from Appendix A, pages 17 through 26 of the study report.

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II. DISCUSSION

A. Investigator's Conclusions - Maximum plasma tyrosine concentration after a single dose of NTBC at 1 mg/kg is approximately 1200 nmol/mL, a level similar to the maximum concentration found in mice in which HPPD is completely inhibited (reference not provided). There is evidence in mice of adaptation, with the tyrosinemia being maintained at a steady-state of approximately 800 nmol/mL. In the human subjects in this study, tyrosine levels were also approximately 800 nmol/mL at 14 days post-dosing, supporting the hypothesis that inhibition of HPPD by NTBC is essentially irreversible and adaptation to the tyrosinemia is similar to that which occurs in mice. Consequently, the tyrosinemia was only marginally increased in the human subjects following the second dose of NTBC.

B. Reviewer's Discussion - In this special study, 10 healthy human male subjects were given a single oral dose of NTBC (purity not reported) at 1 mg/kg in either liquid or capsule (Period 1). After approximately 14 days, patients who received the liquid dose were dosed by capsule and vice versa (Period 2). Plasma tyrosine concentrations were determined from 0–120 hours post-dosing for both periods.

The purpose of the study was to compare the bioavailability of NTBC at therapeutic levels in two different formulations.

This report provides only a summary of the experimental portion of the study. A report from the laboratory performing the clinical portion of the study (Cardiff Clinical Trials Ltd, Cardiff Medicentre, Heath Park, Cardiff, UK) is necessary to complete evaluation of the study.

A single dose of NTBC increased mean plasma tyrosine levels in a linear fashion through approximately 48 hours after dosing, at which time tyrosine levels plateaued. At maximum levels, plasma tyrosine was 1039.6 nmol/mL. This level was increased 935% from a mean pretreatment level of 100.4 nmol/mL. After 14 days recovery, mean plasma tyrosine concentrations had not returned to pre-dosing levels and were still high (808.4 nmol/mL). Administration of the second dose of NTBC increased plasma tyrosine levels to a mean maximum level of 1050.3 nmol/mL. This level is approximately equal to the maximum reached after the first dose, and is 946% greater than the first pre-dose measurement.

This is study is classified **acceptable (non-guideline)** and does satisfy the purposes for which it was intended.

C. Study deficiencies - Subjects were not identified as to which formulation they received first (capsule versus liquid); however, the test subjects did not appear to segregate into two populations based on plasma tyrosine levels, and therefore the dosing formulation was considered not to have had an effect on the bioavailability of NTBC. Details of the dosing and observations made during the clinical phase of the study were not reported.

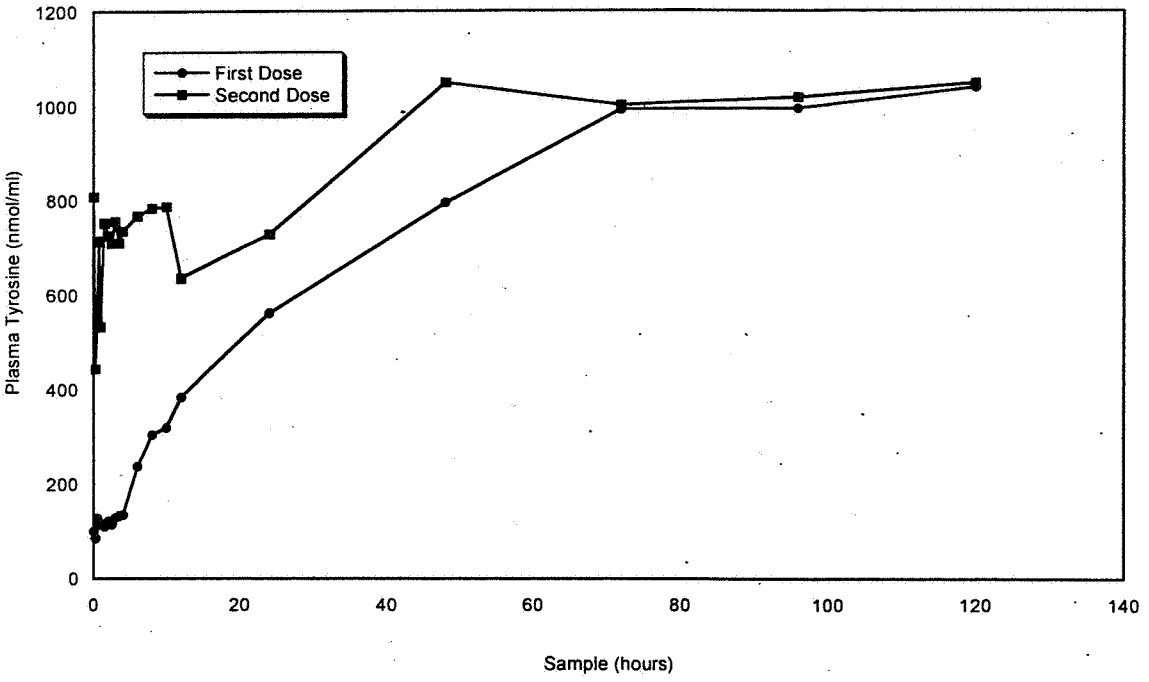

Figure 1. Mean plasma tyrosine concentrations (nmol/ml) in human subjects receiving a single 1 mg/kg oral dose of NBTC at 0 (first dose) and 14 days (second dose).

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