Amino Acids (2007) 32: 459–466
DOI 10.1007/s00726-007-0494-3
Printed in The Netherlands

Amino Acids

Absorption, tissue distribution, metabolism and elimination of taurine given orally to rats

D. W. Sved[1], **J. L. Godsey**[1], **S. L. Ledyard**[1], **A. P. Mahoney**[1], **P. L. Stetson**[1], **S. Ho**[1], **N. R. Myers**[1], **P. Resnis**[1], and **A. G. Renwick**[2]

[1] WIL Research Laboratories, LLC, Ashland, OH, U.S.A.
[2] School of Medicine, University of Southampton, Southampton, U.K.

Received December 12, 2006
Accepted January 11, 2007
Published online February 16, 2007;

Summary. Three biodisposition studies with taurine were performed in male and female adult rats at dosages of 30 and 300 mg/kg. A single oral dose of ^{14}C-taurine was rapidly absorbed, distributed to tissues and excreted unchanged in urine. Elimination of radioactivity from intracellular pools was slow. Pre-treatment of animals for 14 days with unlabelled taurine did not significantly affect the fate of ^{14}C-taurine. At the higher dose there was more extensive excretion combined with a lower percentage of the dose in the carcass, indicating the possibility of saturation of the tubular reabsorption mechanism for taurine. Daily administration of unlabelled taurine for 14 days did not result in an increase in total taurine in the brain. The data indicate that exogenous taurine rapidly equilibrates with endogenous body pools and that any excess is rapidly eliminated by the kidneys.

Keywords: Taurine – Toxicokinetics – Absorption – Tissue distribution – Elimination

Introduction

Taurine (2-aminoethanesulfonic acid) is a non-essential amino acid that is synthesized from cysteine and has a number of important physiological roles, including the regulation of osmotic balance.

Taurine is a highly polar compound and absorption is primarily via transporters in the cell walls of enterocytes (Sharafuddin et al., 1988), with only limited passive diffusion. The distribution of taurine is influenced by its high polarity, which limits diffusion into cells, and entry into cells is largely by specific trans-membrane carriers (Pow et al., 2002). High concentrations of taurine are present endogenously in blood cells, heart, skeletal muscle and the central nervous system. Specific Na^+-dependent carriers are present in these cells and tissues, and these are important in the maintenance of high intracellular to extracellular ratios.

The metabolism of taurine is dominated by its synthesis via oxidation of the SH-group of cysteine and the formation of cysteine sulphinic acid, which undergoes oxidation to cysteic acid followed by decarboxylation to taurine, or decarboxylation to hypotaurine followed by oxidation to taurine. The extent of taurine synthesis in vivo varies widely from species to species; there is a high capacity in rodents and an intermediate capacity in humans, whereas taurine is an essential amino acid in cats (Edgar et al., 1998).

Taurine is eliminated in the urine, and because it can be formed in vivo from the metabolism of other sulphur containing nutrients the excretion can exceed the daily dietary intake (Cho et al., 2000).

The present studies were undertaken to define more clearly the fate of high oral doses of taurine, and in particular the potential for acute or chronic administration to affect the concentrations within the brain.

Materials and methods

Animals and housing

Adult 7–12-week-old male and female Sprague-Dawley Crl:CD®(SD)IGS BR rats were supplied by Charles River Laboratories and were acclimated for approximately 1 week. The animals were maintained in a temperature and humidity controlled facility and given food (PMI Nutrition International Inc., Certified Rodent LabDiet® 5002) and water ad libitum.

Chemicals and reagents

Radiolabelled taurine ([1,2-^{14}C]-taurine – 35 mCi/mmol) was purchased from Moravek Biochemicals Inc. (577 Mercury Lane, Brea, CA 92821,

USA). The radiochemical purity, which was determined by reverse phase HPLC, was stated to be 99.1%. TLC methods were developed during the analysis of urine samples (see Results) and application of this method to the [1,2-^{14}C]-taurine revealed the presence of about 10% as a slightly less polar impurity. Unlabeled taurine (99.9% pure) was provided by Neuber, GmbH, Austria.

Study design and treatment protocols

Study 1

Twelve animals/sex were randomly assigned to each dose group (30 or 300 mg ^{14}C-taurine/kg). Subgroups of 3 males and 3 females were euthanized by carbon dioxide inhalation at 1, 4, 24 and 168 h after administration of a single oral gavage dose of ^{14}C-taurine. Blood and an extensive set of tissues were collected from each animal. Blood was separated into plasma and a cellular fraction by centrifugation. Urine and feces were collected separately from the sub-groups euthanized at 168 h post-dosing over the following intervals: urine collections at 0–6, 6–12, and 12–24 h post-dosing, then daily through 168 h post-dosing; fecal collections at 0–12 and 12–24 h post-dosing, then daily through 168 h post-dosing. Urine and fecal samples were collected on dry ice. After the last collection, the cages were washed with deionized water and the wash retained.

Study 2

Eighteen animals/sex were randomly assigned to each dose group (30 or 300 mg taurine/kg/day). Animals were administered a series of 14 daily oral gavage doses of unlabelled-taurine followed by a single oral gavage dose of ^{14}C-taurine. Subgroups of 3 males and 3 females were euthanized by carbon dioxide inhalation at 1, 4, 24 and 168 h and 14 and 28 days after the ^{14}C-taurine dose. Blood and an extensive set of tissues were collected from each animal. Blood was separated into plasma and a cellular fraction by centrifugation. Urine, feces and cage washings were collected from the sub-group euthanized at 168 h post-dosing as described for Study 1.

Study 3

Nine animals/sex were randomly assigned to each dose group (30 or 300 mg unlabelled taurine/kg/day). Subgroups of 3 males and 3 females were euthanized by carbon dioxide inhalation at 2 h after administration of the 1st, 7th, and 14th oral gavage dose. Blood, brain, heart, kidney, liver, and skeletal muscle were collected from each animal. Plasma was isolated by centrifugation. Control samples were also collected from 3 male and 3 female rats that had not been dosed with taurine.

Doses were prepared in deionized water and administered at a dosage volume of 10 ml/kg using a syringe and ball-tipped cannula. For the radioactive doses, the dosing syringe was weighed before and after delivery of the dose and the difference in weights used to calculate the actual administered dose; unlabelled doses were administered volumetrically.

Analytical methods

Radiochemical methods

a. Determination of total radioactivity: All samples from Studies 1 and 2 were analyzed for total ^{14}C.

Skin samples were solubilized in Soluene®-350 (Packard Instrument Co., Meriden, CT, USA). Fat samples were dissolved in Ultima Gold™ liquid scintillation cocktail (Packard Instrument Co., Meriden, CT, USA). Samples of lung, kidney, liver, brain, muscle, testes, GI tract, and GI tract contents samples were homogenized. Fecal samples were homogenized with deionized water (2 parts feces:1 part water, w/w). Carcass samples were processed using a meat chopper/grinder. All other tissue samples (spleen, pancreas, eyes, adrenal glands, hypophysis, thymus, thyroid gland, mesenteric lymph nodes, mandibular/sublingual glands, bone, testes, prostate, epididymis, ovaries and uterus) were analyzed without prior processing. Each sample or processed sample was prepared for analysis of total ^{14}C radioactivity in duplicate, where possible; heart, spleen, pancreas, eye, adrenal glands, hypophysis, thymus, thyroid, mesenteric lymph node, mandibular/sublingual gland, bone, prostate, epididymis, ovary, and uterus samples were analyzed in their entirety.

Aliquots of known size of each urine, cage wash, and plasma sample and each skin and fat digest were mixed with 10 ml of Ultima Gold™ liquid scintillation cocktail for direct analysis by liquid scintillation counting (LSC) using a Beckman Model LS 6000TA liquid scintillation spectrophotometer (Beckman Instruments Inc., Fullerton, CA, USA). All other samples (or aliquots of samples) were combusted for 4 min using a Harvey Biological Materials Oxidizer (Model OX500 or OX300, R. J. Harvey Instrument Co., Hillsdale, NJ, USA) and radioactivity determined as ^{14}C-CO_2, which was trapped in 15 ml of Permafluor E+:Carbosorb E (2:1, v/v) combined liquid scintillation cocktail and carbon dioxide absorber (Packard Instrument Co., Meriden, CT, USA).

b. HPLC and TLC analysis of radioactivity in test material and urine samples: Urine samples containing more than 5% of the administered dose were analyzed to determine the nature of the radioactivity.

Radio-HPLC analyses – were performed using a Hitachi HPLC system (Hitachi Ltd., Tokyo, Japan) equipped with a 655A-40 autosampler, L-2000 pump, L-4000 variable wavelength UV detector set at 210 nm, and a D-2500 integrator. Radioactivity in the effluent was monitored using a Packard Radiomatic A-515A FLO-ONE/Beta Radioactive Flow Detector (Packard Instrument Co., Meriden, CT, USA) with a 0.5-ml cell. Prior to entering the radioactive flow detector, the column effluent was mixed with Ultima-Flo M scintillation cocktail (Packard Instrument Co., Meriden, CT, USA) pumped at a rate of 3 ml/min. Radioactivity data acquisition and analysis were performed using the Radiomatic flow detector software package (Series 500TR/Ver. 3.60 or 3.65). For radiopurity analyses, a Regis Rexchrom S5-100-ODS (250 × 4.6 mm ID, 5 µm) column was used with a mobile phase of 0.1 M H_3PO_4 at a flow of 1 ml/min. For analysis of radioactivity in urine the same column was used with a gradient mobile phase changing from 95% water:acetic acid (100:2, v/v) and 5% methanol to 5% water:acetic acid (100:2, v/v) and 95% methanol over a period of 30 min. The amount of radioactivity in each peak was reported as a percent of the total radioactivity in the detected peaks. The validity of the radio-HPLC procedure was demonstrated using representative test article and urine samples and achieving quantitative recovery (range 96.6–102%) of the radioactivity applied to the HPLC column.

Radio-TLC analyses – the purity of the ^{14}C-taurine was analyzed using two 2-dimensional chromatography methods. System 1 used a Whatman Silica Gel K6F 60A (250-µm) plate with n-propanol:water (1:1, v/v) as solvent 1 and phenol:water (3:1, v/v) as solvent 2. System 2 used a Merck Cellulose F (100-µm) plate with 1-butanol:acetone:diethylamine (2:2:1, v/v/v) as solvent 1 and isopropanol:formic acid:water (20:1:5, v/v/v) as solvent 2. The presence of urinary metabolites was investigated using a 1-dimensional (1-D) TLC method using a Whatman Silica Gel K6F 60A (250-µm) plate with n-propanol:water (1:1, v/v) as the mobile phase. The plates were analyzed for radioactivity using a Bioscan System 200 Imaging Scanner (Bioscan, Inc., Washington, DC, USA) configured to quantify radioactive beta-emissions in individual lanes or entire plates, as appropriate. Areas of radioactivity were manually selected for integration and peak areas were calculated as a percentage of the total activity in the selected areas.

LC-MS/MS analysis of unlabelled taurine in samples from Study 3

The samples from Study 3 were analyzed for taurine concentration using a validated LC-MS/MS method. Tissue samples were homogenized with 9 ml of 0.05 M borate buffer per g wet weight. After centrifugation, aliquots (50 µl) were transferred to amber conical tubes containing 200 µl

of an aqueous solution of 25% acetonitrile, 22% methanol, and 3% triethylamine by volume and 10 µl of an aqueous solution of internal standard ([1,2-^{13}C]-taurine; 2.0 mg/ml; Cambridge Isotope Laboratories, Inc., Andover, MA, USA). The tubes were mixed, centrifuged (4 °C at 5000 rpm) for 15 min and aliquots (80 µl) were transferred to fresh amber conical tubes containing 40 µl of dansyl chloride solution (1 mg/ml in acetonitrile). The tubes were mixed and heated at 50–60 °C for 45 min. Water (1.08 ml) was added to each tube, and the contents were mixed and transferred to amber autosampler vials for analysis. Separation was achieved using an HPLC gradient from methanol: 0.1 M ammonium acetate (90:10 v/v) to methanol: 0.1 M ammonium acetate (30:70 v/v). Two HPLC/MS systems were used in these analyses: a Hewlett-Packard 1100 liquid chromatograph (Agilent Technologies Inc., Palo Alto, CA, USA) with a Micromass Quattro Ultima™ tandem quadrupole mass spectrometer (Waters Corporation, Milford, MA, USA) and ESI+ interface; and a Waters 2695 liquid chromatograph (Waters Corporation, Milford, MA, USA) with a Micromass Quattro Micro™ tandem quadrupole mass spectrometer (Waters Corporation, Milford, MA, USA) and ESI+ interface.

Toxicokinetic analysis

Toxicokinetic parameters (see Renwick, 2001) were calculated based on the concentrations in plasma. The plasma elimination rate constant was calculated by linear regression of the natural log (ln) of the plasma concentration against the time. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule and extrapolated to infinity using the terminal elimination rate constant.

Results

Study 1

The total recovery of ^{14}C activity after a single oral dose of ^{14}C-taurine was about 90% in males and females at each dose level (Table 1). Urine was the main route of elimination (36–67% of the dose), and significant amounts were recovered in the tissues and carcass. Females excreted more of the dose in urine at both 30 and 300 mg/kg than males, and this was associated with lower retention in the carcass. In addition, the data indicated greater excretion and lower retention at 300 mg/kg compared with the lower dose level. The pattern of elimination in urine (Fig. 1) showed that the main differences between doses and between sexes were during the first 6 h after dosing, when the majority of the renal excretion occurred.

These data indicate that ^{14}C-taurine is rapidly absorbed and excreted, but there is also rapid uptake into tissues where it becomes part of a slowly equilibrating intracellular pool. This explanation is supported by the data for the concentrations of ^{14}C activity in various tissues (Fig. 2). Most tissues (adrenals, bone, hypophysis, kidney, lung, pancreas, skin, spleen, thymus and thyroid) showed a profile similar to that in the liver (Fig. 2) with a clear decrease between 24 and 168 h post-dosing, although different tissues had different tissue: plasma ratios. Other tissues (brain, eyes, fat and muscle) showed a profile similar to the heart (Fig. 2) with a slower increase over the first 24 h post-dosing and little decrease between 24 and 168 h post-dosing.

Non-compartmental linear regression analyses of the concentrations in plasma gave half-lives for the terminal phase in the range 65–130 h (Table 3). The AUCs calculated from the mean data (Table 3) suggest the possibility of non-linear kinetics because the AUC at 300 mg/kg was less than 10 times that at 30 mg/kg.

Study 2

The total recovery and pattern of excretion of ^{14}C activity after a single oral dose of ^{14}C-taurine given to animals pretreated with unlabelled taurine for 2 weeks (Table 2) were similar to Study 1. About 90–100% of the dose was recovered in males and females at each dose level. The urine was the main route of elimination (46–78% of the dose),

Table 1. Elimination of radioactivity over 7 days after a single oral dose of ^{14}C-taurine (Study 1). Results are the mean for 3 animals per sex with the standard deviation given in parentheses

	Percent of ^{14}C dose recovered (as taurine equivalents)			
	Males (30 mg/kg)	Females (30 mg/kg)	Males (300 mg/kg)	Females (300 mg/kg)
Urine	36.19 (4.52)	48.43 (3.27)	58.18 (4.14)	67.32 (1.75)
Feces	4.83 (0.26)	4.45 (0.59)	3.92 (0.43)	4.57 (1.01)
GI tract and contents	2.88 (0.25)	2.71 (0.67)	2.17 (0.17)	1.44 (0.29)
Tissues[a]	2.96 (0.42)	2.63 (0.58)	1.88 (0.11)	1.46 (0.13)
Blood[a]	0.07 (0.01)	0.05 (0.01)	0.04 (0.02)	0.03 (0.02)
Carcass[b]	40.98 (1.09)	31.32 (1.42)	25.08 (1.88)	16.39 (2.43)
Cage wash	0.08 (0.01)	0.16 (0.04)	0.06 (0.02)	0.09 (0.06)
Total recovered	88.0 (2.6)	89.7 (2.4)	91.3 (3.8)	91.3 (5.3)

GI Gastro-intestinal
[a] Percent recovered in removed samples
[b] Percent in the residual carcass

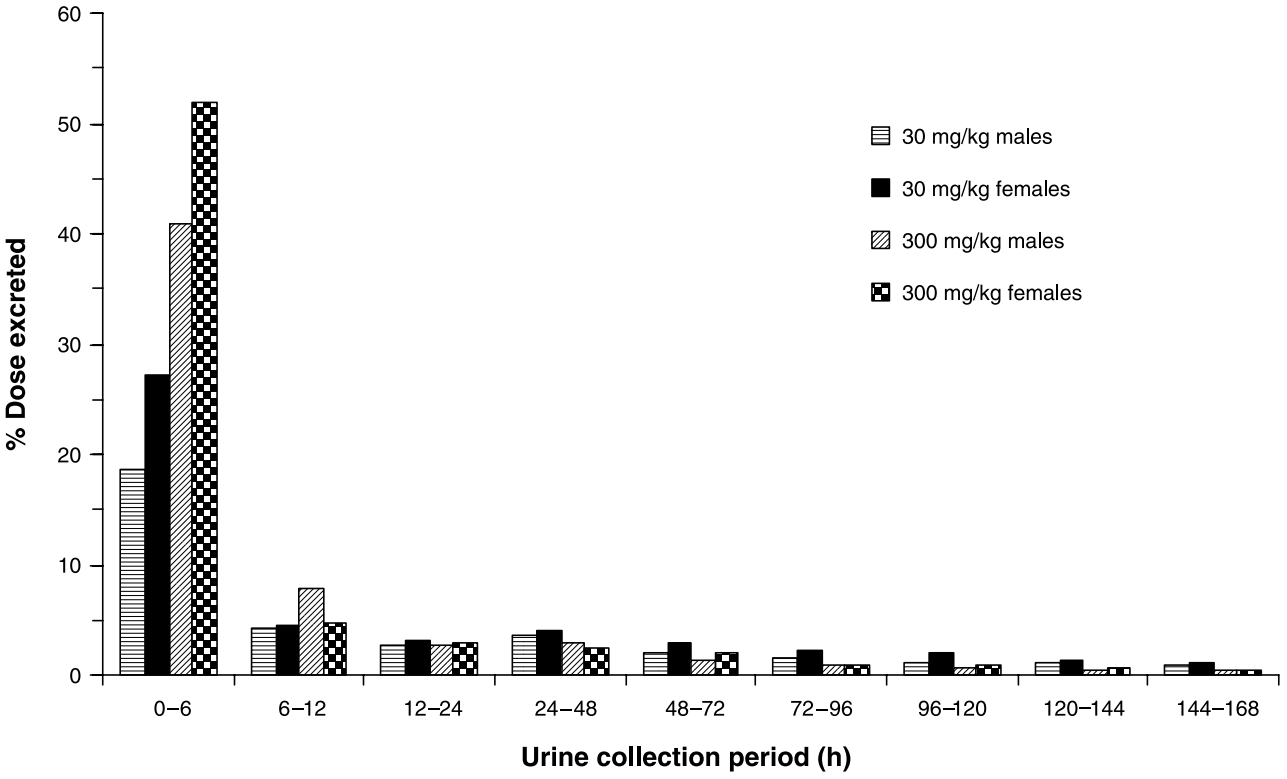

Fig. 1. Urinary excretion of radioactivity after a single oral dose of ^{14}C-taurine (Study 1). Each value is the mean of 3 animals per sex at each time point

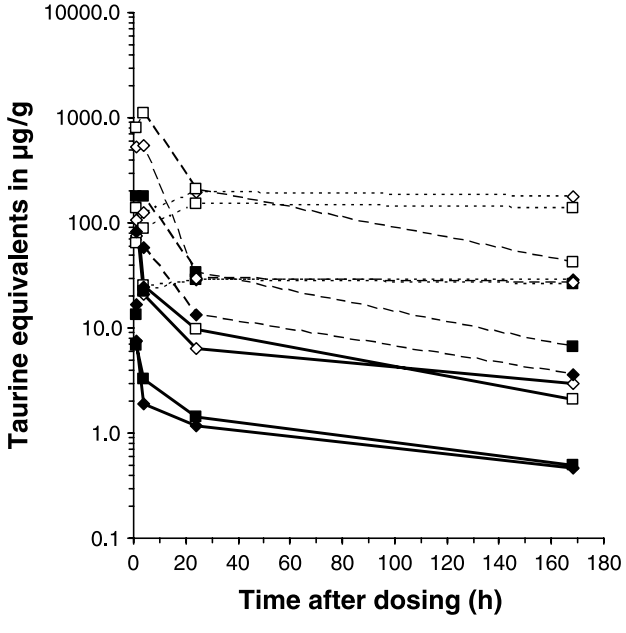

Fig. 2. Concentrations of radioactivity expressed in taurine equivalents in plasma (solid lines), heart muscle (dotted line) and liver (dashed line) after a single oral dose of ^{14}C-taurine (Study 1). Each value is the mean of 3 animals per sex at each time point. 30 mg/kg – Filled symbols; 300 mg/kg – open symbols; diamonds – males; squares – females

and significant amounts were recovered in the tissues and carcass. The trend towards greater urinary excretion and lower tissue retention at 300 mg/kg seen in Study 1 was also apparent in these data, but there was no indication of the possible sex difference suggested by Study 1. The pattern of elimination in urine (Fig. 3) shows that the excretion during the first 6 h after the radiolabelled dose following a period of pre-treatment was similar to that after the radiolabelled dose alone (Fig. 1), indicating that pre-treatment with high daily doses did not affect the absorption, tissue distribution or excretion of taurine. This conclusion was supported by the tissue concentration data (Fig. 4), which were essentially the same as following a single dose (Fig. 2). The tissue concentrations of taurine equivalents over 168 h after the radiolabelled dose following pre-treatment (Study 2) were essentially the same as found after the radiolabelled dose alone (Study 1). The negligible elimination from tissues such as brain, eyes, fat, heart and muscle over 168 h post-dosing was confirmed in Study 2, but the extended period of sampling demonstrated a very slow elimination phase from these tissues. Importantly, the concentrations of ^{14}C activity in brain as measured over 168 h post-dosing were not affected by pre-treatment with unlabelled taurine (Fig. 5).

Table 2. Elimination of radioactivity over 7 days after a single oral dose of ^{14}C-taurine given following a period of repeated oral dosing at the same levels of treatment (Study 2). Results are the mean for 3 animals per sex with the standard deviation given in parentheses

	Percent of ^{14}C dose recovered (as taurine equivalents)			
	Males (30 mg/kg)	Females (30 mg/kg)	Males (300 mg/kg)	Females (300 mg/kg)
Urine	45.86 (5.39)	51.06 (7.83)	77.72 (7.16)	72.31 (4.12)
Feces	4.82 (0.39)	4.04 (0.51)	4.40 (0.74)	4.04 (0.29)
GI tract and contents	1.78 (0.14)	2.27 (0.62)	0.86 (0.17)	1.72 (0.76)
Tissues[a]	1.97 (0.27)	2.15 (0.25)	0.92 (0.10)	1.43 (0.23)
Blood[a]	0.05 (0.01)	0.03 (0.01)	0.02 (0.00)	0.03 (0.01)
Carcass[b]	33.62 (1.43)	30.13 (1.98)	15.64 (1.41)	15.09 (1.79)
Cage wash	0.12 (0.04)	0.18 (0.05)	0.08 (0.04)	0.09 (0.01)
Total recovered	88.2 (6.0)	89.9 (6.6)	99.7 (7.1)	94.7 (1.3)

GI Gastro-intestinal
[a] Percent recovered in removed samples
[b] Percent in the residual carcass

Table 3. Toxicokinetic parameters derived from plasma data by linear regression analysis applied to the terminal, apparently linear phase (usually only 2 or 3 data points). The results were calculated using the mean concentrations for 3 animals of each sex at each time point

Sex	Dose (mg/kg)	Study 1		Study 2		Study 2	
		Half-life (24–168 h)	AUC	Half-life (24–168 h)	AUC	Half-life (168–672 h)	AUC
Male	30	107	236	78	267	240	386
Female	30	96	272	74	259	479	432
Male	300	130	1760	63	2031	302	2652
Female	300	65	1706	82	2294	225	2783

Half-life is in hours – the time points used to calculate the terminal half-life are shown in parentheses; AUC is in (μg/ml) ∗ h and is the total AUC extrapolated to infinity using the estimated terminal half-life

Non-compartmental linear regression analyses of the concentrations in plasma using data between 24 and 168 h post-dosing only gave apparent half-lives in the range 63–82 h, values that were similar to the results for Study 1 calculated using the same time points (Table 3). The terminal half-lives calculated using data for the period of 168–672 h post-dosing were considerably longer at 225–479 h (Table 3), as can be predicted from the data in Fig. 4. Half-lives and AUC values are given in Table 3. The data in Table 3 for Study 2 also support the possibility of non-linear kinetics at the doses studied since the systemic exposure after oral dosage, as indicated by the AUC, showed a less than 10-fold increase for a 10-fold increase in dose.

Study 3

The concentrations of taurine in plasma, liver, kidney, brain, heart and muscle for control animals and at 2 h after dosing in animals receiving 1, 7, or 14 doses of unlabeled taurine at 30 or 300 mg/kg/day are presented in Table 4. Overall the concentrations in the different tissues did not show major differences between controls and treated animals, and were not greatly influenced by dose level or duration of treatment. The concentrations in plasma and kidneys were higher in treated animals compared to controls, but there was no indication of accumulation with repeated dosing. The concentrations in livers and male muscle appeared to increase with repeated dosing, but there was no such trend in female muscle. Importantly there were no indications of treatment-related changes in the concentrations in the brain, either in relation to dose level or duration of treatment.

Biotransformation (Studies 1 and 2)

Urine samples containing more than 5% of the administered radioactivity were analyzed using HPLC and TLC. A gradient elution radio-HPLC method indicated that there was only one radioactive component in the urine samples,

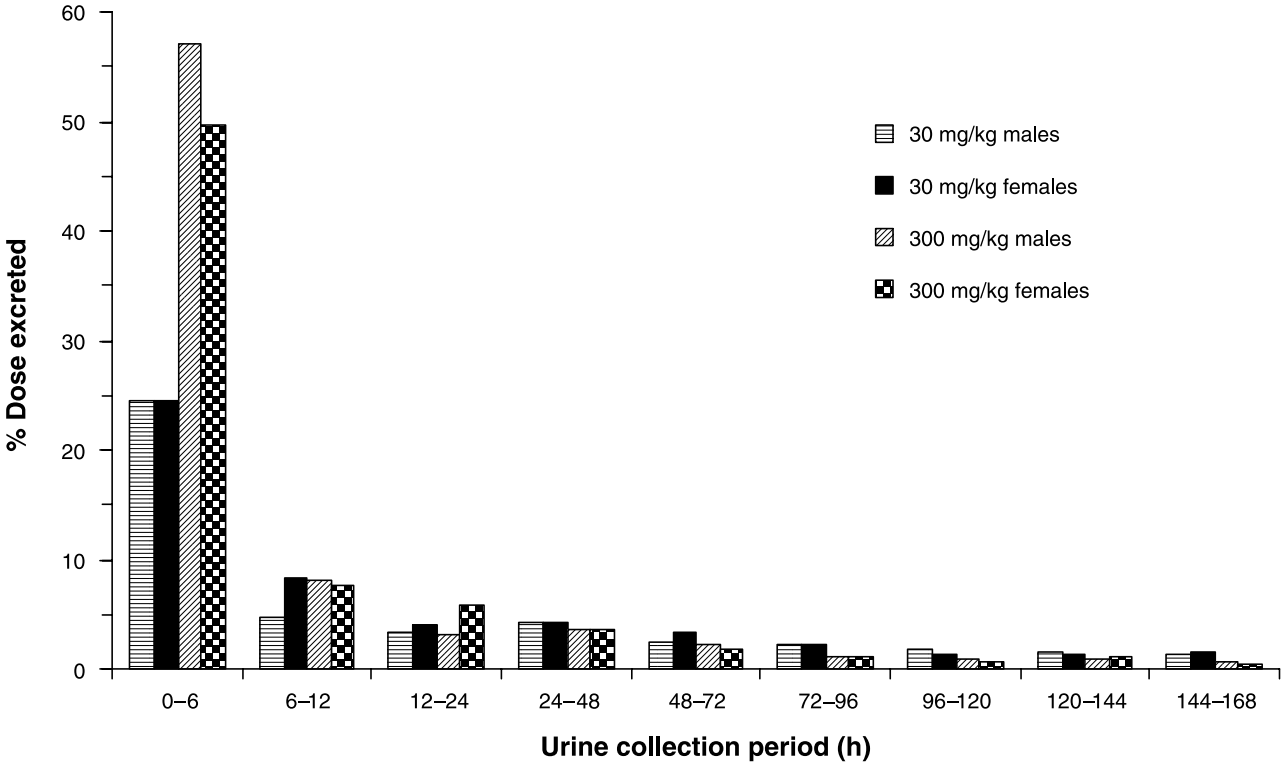

Fig. 3. Urinary excretion of radioactivity after an oral dose of ^{14}C-taurine given following a period of repeated oral dosing at the same levels of treatment (Study 2). Each value is the mean of 3 animals per sex at each time point

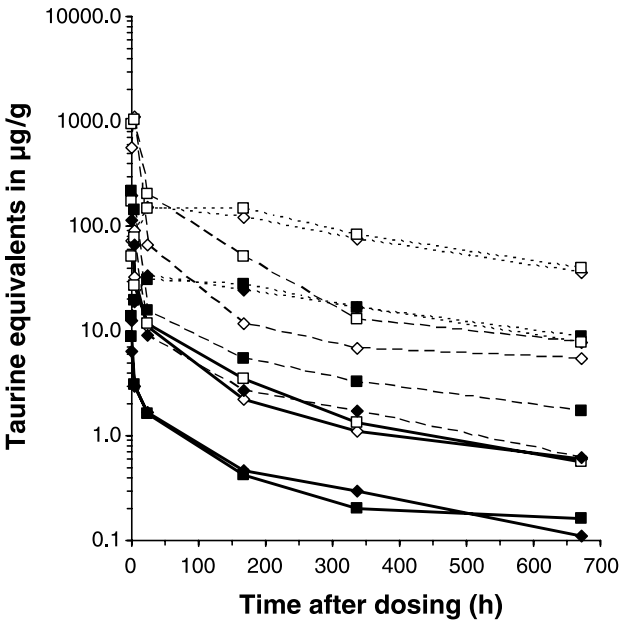

Fig. 4. Concentrations of radioactivity expressed in taurine equivalents in plasma (solid lines), heart muscle (dotted line) and liver (dashed line) after an oral dose of ^{14}C-taurine given following a period of repeated oral dosing at the same levels of treatment (Study 2). Each value is the mean of 3 animals per sex at each time point. 30 mg/kg – Filled symbols; 300 mg/kg – open symbols; diamonds – males; squares – females

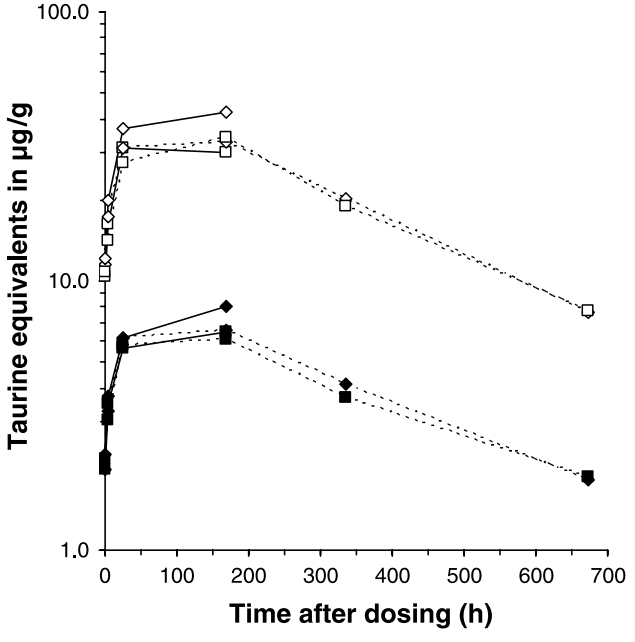

Fig. 5. Concentrations of radioactivity expressed in taurine equivalents in brain after a single oral dose of ^{14}C-taurine (solid lines – Study 1) and after an oral dose of ^{14}C-taurine given following a period of repeated oral dosing at the same levels of treatment (dotted lines – Study 2). Each value is the mean of 3 animals per sex at each time point. 30 mg/kg – Filled symbols; 300 mg/kg – open symbols; diamonds – males; squares – females

Table 4. Concentrations of taurine in rats given repeated doses (Study 3)

Group	Day[a]	Taurine concentration					
		Plasma (μg/g)	Liver (mg/g)	Kidney (mg/g)	Brain (μg/g)	Heart (mg/g)	Muscle (mg/g)
Males							
Controls	*None*	*31 (3)*	*0.52 (0.47)*	*1.41 (0.45)*	*737 (11)*	*1.95 (0.32)*	*1.56 (0.05)*
30 mg/kg	1	36 (13)	0.76 (0.58)	1.12 (0.034)	709 (37)	2.22 (0.12)	1.76 (0.31)
30 mg/kg	7	51 (17)	1.03 (0.15)	1.79 (0.80)	649 (73)	2.22 (0.28)	2.20 (0.19)
30 mg/kg	14	33 (11)	0.91 (0.37)	1.36 (0.17)	807 (130)	2.13 (0.31)	2.52 (1.32)
300 mg/kg	1	72 (9)	1.30 (0.53)	2.11 (0.26)	757 (35)	2.29 (0.16)	1.73 (0.21)
300 mg/kg	7	88 (25)	1.41 (0.40)	1.99 (0.08)	810 (112)	2.28 (0.19)	2.04 (0.14)
300 mg/kg	14	72 (43)	1.53 (1.03)	1.34 (0.68)	790 (22)	2.36 (0.37)	2.26 (0.14)
Females							
Controls	*None*	*25 (6)*	*0.94 (0.84)*	*1.15 (0.18)*	*659 (32)*	*2.25 (0.17)*	*2.10 (0.23)*
30 mg/kg	1	32 (9)	0.85 (0.57)[2]	1.59 (0.31)	674 (12)	2.00 (0.23)	2.27 (0.08)
30 mg/kg	7	51 (9)	1.29 (0.68)	1.29 (0.37)	628 (35)	2.02 (0.61)	2.17 (0.33)
30 mg/kg	14	34 (4)	2.00 (0.20)	1.65 (0.78)	696 (23)	1.97 (0.01)	1.97 (0.12)
300 mg/kg	1	85 (6)	2.71 (0.38)	1.92 (0.20)	610 (16)	2.39 (0.57)	1.93 (0.13)
300 mg/kg	7	90 (27)	2.21 (1.13)	1.95 (0.21)	638 (31)	2.34 (0.20)	1.97 (0.11)
300 mg/kg	14	88 (12)	3.51 (0.80)	1.57 (0.10)	720 (91)	2.17 (0.17)	2.16 (0.09)

The animals were euthanized 2 h after the dose on the day stated. The results are the mean for 3 animals per sex (except where the number is given as a superscript) with the standard deviation given in parentheses
[a] Day of treatment

with the retention time of taurine. Subsequently, the 1-D TLC system demonstrated the presence of two radioactive components in the urine samples. The major component corresponded to taurine, but there was a second, less polar compound present that was found to have the same chromatographic characteristics as the radiolabelled impurity detected subsequently in the ^{14}C-taurine (which had not been separated by the HPLC methods used in this study or by the producers). Urine samples from 0–6 h post-radiolabelled dose contained approximately equal amounts of radioactivity in each component, while later time points (24–48 h) were predominantly taurine. These data suggest that the radiolabelled impurity in the ^{14}C-taurine was eliminated more rapidly than taurine despite its lower polarity, probably because it was not a substrate for tissue sequestration. Because of its more rapid elimination, the pattern of tissue distribution and the slow elimination from tissues based on total radioactivity measurements would not have been affected greatly by the presence of the impurity. No other radioactive compounds were detected, showing that there was no significant urinary excretion of any metabolites of taurine.

Discussion

Studies 1 and 2 showed that ^{14}C-taurine is rapidly absorbed from the gastro-intestinal tract, distributed widely to tissues, and undergoes elimination unchanged in the urine. Both studies indicated more extensive elimination of the higher dose during the first 6 h after dosing. This could be due to either more extensive absorption or greater renal excretion at the higher dose level than at the lower dose level. More extensive absorption is unlikely because the greater urinary excretion at the higher dose was associated with lower tissue concentrations. Increased renal excretion of high exogenous doses would be consistent with saturation of a reuptake process that is used to maintain a constant body load. Seven different transporters for amino acids have been reported in the renal tubule, and taurine undergoes active reabsorption via a Na^+/Cl^--coupled transporter that is specific for beta-amino acids (Zelikovic and Chesney, 1989; Jones et al., 1992; Zelikovic and Budreau-Patters, 1999). The taurine-transporter is saturable and has a high affinity but low capacity (Dantzler and Silbernagl, 1976). The physiological significance of the taurine-transporter is shown by the increase and decrease in its expression that are associated with low and high dietary intakes of sulphur amino acids (Chesney et al., 1989; Han et al., 1996).

The similarity of the data from Studies 1 and 2 shows that a period of pre-treatment with up to 300 mg/kg/day for 14 days did not affect the biodisposition of an oral dose of radiolabelled taurine.

The data from Study 3 show that the concentrations of taurine in tissues do not significantly increase over a 2-week period of daily administration of 300 mg/kg. These data may seem to contradict the data from Studies 1 and 2, which showed rapid uptake by tissues and slow elimination of the ^{14}C-activity especially from some tissues, such that accumulation would be predicted. While this would be true for a xenobiotic compound, this simple interpretation does not apply to exogenous doses of a non-essential endogenous compound, the levels of which are under homeostatic control. The data are consistent with carrier-mediated uptake of taurine into tissues where it becomes part of the endogenous intracellular pool. The rate of elimination of intracellular taurine will depend on the rate of turnover of the intracellular pool for that particular tissue.

The study was undertaken to define the general biodisposition of exogenous taurine. The apparent discrepancy between the presence of significant increases in concentrations of ^{14}C-activity in the brain after doses of ^{14}C-taurine (Fig. 5) with the absence of a significant increase in the brain concentrations of taurine at 2 h after dosing with unlabelled taurine can be explained by the size of the intracellular pool within the brain and the probability that the ^{14}C-taurine would have been exchanged for unlabelled taurine, so that the total concentration would not change. Taurine crosses the blood–brain barrier into the brain via a saturable Na^+/Cl^--dependent transporter (Chung et al., 1994; Tamai et al., 1995), so that the concentrations in the brain will not be directly proportional to the concentrations in the general circulation at high plasma concentrations (Stummer et al., 1995).

Overall the results from these studies show that the biodisposition of exogenous taurine is dominated by equilibration of part of the dose with the endogenous pools of taurine that are present in body tissues, and by the rapid renal excretion of the remainder of the dose.

References

Chesney RW, Jolly K, Zelikovic I, Iwahashi C, Lohstroh P (1989) Increased Na^+-taurine symporter in rat renal brush border membranes: preformed or newly synthesised? FASEB J 3: 2081–2085

Cho KH, Kim ES, Chen JD (2000) Taurine intake and excretion in patients undergoing long term enteral nutrition. Adv Exp Med Biol 483: 605–612

Chung SJ, Ramanathan V, Giacomini KM, Brett CM (1994) Characterization of a sodium-dependent taurine transporter in rabbit choroid plexus. Biochim Biophys Acta 1193: 10–16

Dantzler WH, Silbernagl S (1976) Renal tubular reabsorption of taurine, gamma-aminobutyric acid (GABA), and beta-alanine studied by continuous microperfusion. Pfluger's Arch 367: 123–128

Edgar SE, Kirk CA, Rogers QR, Morris JG (1998) Taurine status in cats is not maintained by dietary cysteinesulfinic acid. J Nutr 128: 751–757

Han X, Chesney RW, Budreau AM, Jones DP (1996) Regulation of expression of taurine transport in two continuous renal epithelial cell lines and inhibition of taurine transporter by a site-directed antibody. Adv Exp Med Biol 403: 173–191

Jones DP, Miller LA, Budreau A, Chesney RW (1992) Characteristics of taurine transport in cultured renal epithelial cell lines: asymmetric polarity of proximal and distal cell lines. Adv Exp Med Biol 315: 405–411

Pow DV, Sullivan R, Reye P, Hermanussen S (2002) Localization of taurine transporters, taurine and (3H) taurine accumulation in the rat retina, pituitary and brain. Glia 37: 153–168

Renwick AG (2001) Toxicokinetics: Pharmacokinetics in toxicology. In: Hayes AW (ed) Principles and methods of toxicology. Taylor & Francis, Philadelphia, pp 137–191

Sharafuddin M, Nassar GM, Nassar CF (1988) Taurine transport across the small intestine of adult and suckling rats. Comp Biochem Physiol A 91: 33–36

Stummer W, Betz AL, Shakui P, Keep RF (1995) Blood–brain barrier taurine transport during osmotic stress and in focal cerebral ischemia. J Cerebr Blood Flow Metab 15: 852–859

Tamai I, Senmaru M, Terasaki T, Tsuji A (1995) Na(+)- and Cl(−)-dependent transport of taurine at the blood–brain barrier. Biochem Pharmacol 50: 1783–1793

Zelikovic I, Budreau-Patters A (1999) Cl^- and membrane potential dependence of amino acid transport across the rat renal brush border. Mol Genet Metabol 67: 236–247

Zelikovic I, Chesney RW (1989) Sodium-coupled amino acid transport in renal tubule. Kidney Int 36: 351–359

Authors' address: D. W. Sved, Ph.D., Director of Metabolism and Analytical Chemistry, WIL Research Laboratories, LLC, 1407 George Road, Ashland, OH 44805, U.S.A.,
Fax: +1-419-289-8750, E-mail: sved@wilresearch.com