A preclinical study to model taurine pharmokinetics in the undernourished rat

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Abstract

Malnutrition is a common feature of chronic and acute diseases, often associated with a poor prognosis, including worsening of clinical outcome, owing, among other factors, to dysfunction of the most internal organs and systems affecting the absorption, metabolism and elimination of drugs and nutrients. Taurine is involved in numerous biological processes and is required in increased amounts in response to pathological conditions. The aim of this study was to describe the behaviour of taurine in well-nourished (WN) rats and to analyse the influence of protein–energy undernutrition on the pharmokinetic (PK) parameters of taurine, using a PK model. Wistar rats were randomly distributed into two groups, WN and undernourished (UN), and taurine was administered intravenously or orally at different doses: 1, 10 and 100 mg. Population pharmokinetic modelling of plasma levels was performed using the NONMEM 7.2 program. Several distribution and absorption models were explored in combination with dose and/or time covariate effects. Covariates such as nutritional status, serum albumin, body weight and score of undernutrition were used. A two-compartment population pharmokinetic model with zero-order endogenous absorption models were explored in combination with dose and/or time covariate effects. Covariates such as nutritional status, serum albumin, body weight and score of undernutrition were used. A two-compartment population pharmokinetic model with zero-order endogenous formation, passive absorption, first-order kinetics distribution and non-linear elimination with parallel Michaelis–Menten excretion and reabsorption processes best described taurine pharmokinetics. Undernutrition acted as a covariate reducing the V_max of the active elimination process. Data analysis showed linear absorption and distribution, and non-linear elimination processes for taurine. Elimination of taurine was reduced in UN animals, suggesting that the reabsorption process via the secretion transporter was modified in that group.

Key words: Malnutrition; Taurine; Pharmokinetic modelling; In vivo studies

Malnutrition is a range of deficiency states, from mild to severe, defined as a range of pathological conditions arising from coincident deficiency of protein and energy content in varying proportions, being a prevalent clinical condition in many hospitalised patients14. It is estimated that 50% of adult patients admitted to hospitals have malnutrition, making it one of the most prevalent comorbidities in this population15. Malnutrition derives from clinical, social and cultural factors, and its association with higher morbidity and mortality rates, longer length of stay and higher hospital costs has been widely demonstrated in the literature16-20.

Individuals with protein–energy undernutrition have both reduced adipose and lean tissue, reductions in cardiac output with reduced hepatic blood flow and glomerular filtration rate21. Considering the wide range of pathophysiological derangements in patients with undernutrition (UN), the pharmokinetics of many of the drugs used for their treatment is likely to be affected, which may require dose modifications22-24. Taurine (2-aminoethanesulphonic acid) is a conditionally essential sulphur-amino acid. A balanced diet provides most taurine either directly or by synthesis in the liver and brain from methionine or cysteine in the presence of vitamin B6. This amino acid is eliminated in urine. As it can be formed in vivo from the metabolism of other sulphur-containing nutrients, its excretion may exceed the daily dietary intake25. In pathophysiological status, the endogenous production of taurine from its precursors is limited and the excretion can be incremented26, and thus the intake of taurine should be increased to maintain physiological levels.

Taurine is involved in numerous biological and physiological processes, including the regulation of the osmotic balance. Taurine participates, for instance, in bile acid formation and neuronal development, as well as function27. It exerts antioxidant and anti-inflammatory actions, as well as anti-arrhythmic/ionotropic/chronotropic ones, besides constituting a central nervous system neuromodulator. The positive effects of taurine on thyroid dysfunction and renal oxidative damage28,29, epilepsy30,31.

Abbreviations: IV, intravenous; UN, undernourished; WN, well-nourished.

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ischaemia, obesity, hypercholesterolaemia, diabetes, hypertension, myocardial infarction, hepatic inflammatory diseases and neurotoxicity have also been reported. Hence, taurine is widely used as a nutraceutical and it is occasionally used as a drug.

Thus far, little is known about the pharmacokinetics of taurine after oral administration. Such information is essential if a regimen for administration of this agent as a nutraceutical in enteral diets or as therapeutic substance is designed – for example in treating the adverse effects of nickel in the nervous system or after paracetamol poisoning. A review of the literature revealed only very few reports concerning the pharmacokinetics of taurine. One study performed by Rakotoambinina et al. was carried out using a constant intravenous (IV) infusion of labelled taurine at rates of either 2 or 3 μmol/kg per h with or without a priming dose in six healthy patients, and in another study by Ghandforoush-Sattari et al. 4 g of taurine was orally administered to eight healthy volunteers. Only scarce information was found on oral administration of taurine in undernutrition, and no records were found about taurine pharmacokinetics in malnutrition.

The present study was undertaken to determine the preclinical pharmacokinetic model of taurine after oral and intravenous administration and to investigate the influence of nutritional status on the pharmacokinetics of this amino acid.

Methods

Protocol, animals and experimental procedures

Male Wistar rats were used in accordance with 2010/63/EU directive of 22 September 2010 regarding the protection of animals used for scientific experimentation. All the assays described in the present study adhered to the Principles of Animal Care and were approved by the Institutional Ethics Committee of University of Valencia (Spain) according to RD 1201/2005 (code A1326906234491).

A parallel study was designed in which a single dose of taurine was administered either IV or orally to each group of rats. A total of sixty-four male Wistar rats, 8-9 weeks of age, with a mean weight of 235·5 (so 7·9) g, a mean serum albumin of 3·4–6·5 g/l and a mean serum cholesterol of 1·29 (so 0·324) g/l were used. Animals were placed in individual polyethylene cages (22 × 22 × 16 cm) in a controlled room (22–23°C, 50–60% humidity) under a 12 h light–12 h dark cycle. Subjects were randomly assigned to one of two groups: well-nourished (WN) (regular nutrition diet/WN, n 32) and UN (protein–energy restricted diet/UN, n 32). Both groups were allowed free access to water, but their food intake was controlled. The WN group was subjected to a standard pelleted diet (2014 from Harlan laboratory) that fulfilled the normal daily requirements of a rat (14% proteins, dose of diet intake per d: 20 g/251·9 kJ) during an adaptation period that lasted 23–25 d. The UN group received a diet that was altered in protein, carbohydrate and fat content (TD 99168 from Harlan laboratory; 5% proteins, dose of diet intake per d: 10 g/159·5 kJ) for the same period of time.

The rats of both groups (WN and UN) were weighed on a daily basis and serum albumin and serum total cholesterol were quantified once a week using standard commercial kits (QCA Laboratory).

The main biometrical parameters used for the assessment of the nutritional status were weight and serum albumin. Animals of the UN group were considered malnourished if, at the end of the adaptation period, the weight was below 80% of the weight reached in the WN animal group and serum albumin was below 23 g/l. Serum total cholesterol values were also recorded.

The pharmacokinetic study was performed at the end of the adaptation period. For this purpose, rats from both nutritional status (WN or UN) were randomly allocated into different groups based on the dose and route of taurine administration (IV or oral). This protocol resulted in a total of twelve groups, consisting of between four and six animals (Table 1).

The day before administration, rats were subjected to jugular vein cannulation with a 12-cm-long fragment of medical-grade silicone tubing (Silastic, inner diameter: 0·6 mm; outer diameter: 0·94 mm; Dow Corning Co.). Anaesthesia and analgesia were induced before surgery with intraperitoneal thiopental Na solution 10% (w/v) at a dose of 30 mg/kg (Doletal®, Vetoquinol) and subcutaneous butorfanol tartrate (Torbugsic®; Pfizer). Under anaesthesia, a 3–4-cm section of the cannula was introduced into the jugular vein in the direction of the heart and the free end was subcutaneously conducted to the dorsal base of the neck, at which point the cannula emerged. The exter- iorised end was then closed with a polyethylene plug. The cannula was filled with heparinised (0·2 g/l) saline solution. After surgery, animals were maintained in non-fasting conditions overnight with water freely available.

Taurine administration and blood sample collection

Taurine was purchased from Sigma-Aldrich® (Welwyn Garden City). A total of sixty-four animals was used in the study. Solutions were prepared by dissolving the corresponding amount of the amino acid in saline solution.

To facilitate the blood sampling of conscious rats, a 15-cm-long silicon tube (bridge-tubing) was connected to the free end of the cannula. For oral administration, rats were subjected to gastric intubation with all the groups receiving 1 ml of their assigned preparation.

Table 1. Experimental design

<table>
<thead>
<tr>
<th>Groups</th>
<th>Route of administration</th>
<th>Taurine dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Intravenous</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Intravenous</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Intravenous</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Oral</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Oral</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>Oral</td>
<td>100</td>
</tr>
<tr>
<td>UN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Intravenous</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Intravenous</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>Intravenous</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>Oral</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Oral</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Oral</td>
<td>100</td>
</tr>
</tbody>
</table>

WN, well-nourished; UN, undernourished.
After IV or oral administration, blood samples were taken using heparinised syringes from the jugular vein cannula at the scheduled time. After each sampling time, the blood volume was replaced with the same volume of saline solution. After collection, each blood sample was centrifuged at 5000 rpm for 5 min and the plasma was transferred to polypropylene tubes and stored at -20°C until taurine quantification. To achieve the deproteinisation of samples, 5-sulfosalicylic acid was used as previously described. Samples stored in these conditions remained stable for at least one month (the remaining taurine concentration at this time was above 95%).

Analytical procedures

Plasma samples were assayed for taurine content by HPLC, with fluorimetric detection taking place after derivatisation with OPA-MPA (λex = 290 nm, λem = 589 nm). The buffer used to prepare the mobile phase consisted of 9 mM potassium dihydrogen phosphate and 0.5 M triethylamine, adjusted to pH 6.9 with KOH. The mobile phase was prepared by mixing this buffer with a mixture of organic solvents (methanol–acetone, 90:10) in 55/45 (v/v). A reversed-phase column was used (UltraBase C18 3 mm × 6 mm). A flow rate of 0.9 ml/min was used, and 50 μl of the clear supernatants was injected into the chromatograph. Calibration curves covering the whole range of taurine concentrations in the plasma samples (from 50 to 750 μM) were prepared in triplicate. The taurine peak area was measured in each sample and correlated with the amino acid concentration. Excellent plots correlating the peak areas and amino acid concentrations were obtained (r2 > 0.999). The accuracy and precision of the method were confirmed using four concentrations covering the range of 0.1 to 20 μM for taurine samples. The results obtained were considered fully acceptable.

Pharmacokinetic modelling and statistical analysis

A stepwise population pharmacokinetic approach was followed by using a non-linear mixed effects model and the first-order estimation method, implemented with NONMEM, version VI, in conjunction with a G77 FORTRAN compiler and Wings for NONMEM. Different subroutines were used, namely ADVAN 3, 11 and 9. The experimental data used to build the model were total plasma concentration of taurine.

As the taurine concentration in plasma is owing to both internal regulation and external particular uptake, for the modelling, two input constants were considered: a zero order (Q0 (mg/h)) as representative of an internal equilibrium of synthesis and degradation, and a second input constant to characterise the uptake from oral administration, modelled considering a passive or an active process.

Pharmacokinetic modelling was performed from an empiric and mechanistic perspective. The empiric approach allowed deciding whether the pharmacokinetic parameters depend on the dose administered and the mechanistic approach was performed to select the kinetics of each ADME process. The model was developed sequentially, so that whenever modifications had to be made to the base structure of the model a backwards procedure was performed. Data were also incorporated in a sequential manner. The analysis consisted of the following steps:

1. Step 1: TAU IV data from groups 1, 2 and 3 (WN).
2. Step 2: TAU IV data from groups 7, 8 and 9 (UN).
3. Step 3: TAU IV data from groups 1, 2, 3, 7, 8 and 9 (WN and UN).
4. Step 4: TAU IV data from groups 1, 2, 3, 7, 8, 9 and oral data from groups 4, 5, 6 and 10, 11 and 12 (WN and UN).

In steps 1 and 2, the selection of the compartmental model (one compartment or two compartments) was made and non-linearity in the distribution or elimination processes was assayed. Step 3 was implemented to optimise the model characterising the non-linear processes detected in previous steps and also evaluating the influence of the nutritional status on the pharmacokinetic parameters (distribution and excretion). In the last stage of model development (step 4), the values for disposition parameters were fixed at those obtained in step 3, as the addition of oral data did not affect them. Then, the oral absorption process was studied and the influence of the nutritional status on taurine absorption and bioavailability was tested.

Inter-individual variability (IV) in pharmacokinetic parameters and residual error in plasma concentration was modelled with exponential equations (Equations (1) and (2), respectively):

\[ \theta_i = \theta_0 + \epsilon_i \sim N(0, \sigma \theta^2) \]  
\[ y_i = f(\theta_i, D_i, x_i) + \epsilon_i \sim N(0, \sigma^2) \]  

In Equation (1), \( \theta_i \) is the pharmacokinetic parameter \( \theta \) of the individual, \( \bar{\theta} \) the mean population value of this pharmacokinetic parameter and \( \epsilon_i \) the IV of a population (N) with a mean randomly distributed around zero and an estimated variance of \( \sigma^2 \). The need to include inter-IV terms was evaluated for all parameters.

For the residual error calculation, Equation (2), \( f(\theta_i, D_i, x_i) \) represents the individual predicted concentration by means of a particular pharmacokinetic model \( f \), with individual pharmacokinetic parameters, \( \theta_i \), dose, \( D_i \) and time, \( t \), at which concentrations of the amino acid were evaluated (dependent variable, \( x_i \) ) and were modelled in terms of epsilon (\( \epsilon \)) variables. Each \( \epsilon \) variable was assumed to have a mean of zero and an estimated variance \( \sigma^2 \). A slope-intercept error model was used where the residual variability \( \sigma^2 \) of the exponential term was interpreted as a CV and the added component as standard deviation.

In the selection of the best model, the minimum value of objective function (MOFV) provided by NONMEM was adopted. For hierarchical models, the difference between objective function values is distributed as \( \chi^2 \) which allows the best model to be selected. A P level of 0.01 was chosen for accepting a more complex model over a reduced one. For hierarchical models differing by one or two parameters, the corresponding differences in the objective function values are 6-63 and 9-21, respectively. Precision in the estimation of the parameter values, quantified as the relative standard error (%) and residual error, were also evaluated in order to select the final model. The graphical goodness of fit analysis was evaluated through the use of SPlus for Windows, version 7.0 (Insightful) and R (version R-3.1.2).
Model evaluation was performed by means of a visual predictive check and the bootstrap resampling technique. For Visual predictive check, simulations of taurine concentration-time profiles for 200 simulated populations were performed using the final model, and each model parameter was estimated including IV. For each group, the concentration-time profiles corresponding to the 5th, 50th and 95th percentiles were represented together with the corresponding observations. Similarly, the bootstrap resampling technique was used as an internal method to validate the final model. From the original data set, 1000 replicates were generated by sampling randomly with replacement, and the final population pharmacokinetic model was fitted repeatedly to each replicate using the bootstrap option of Wings for NONMEM V package (Holford, version 222, May 2001). The mean and median parameter estimates and their 95% CI were obtained from the resampling technique. For Visual predictive check and the bootstrap resampling technique. For Visual predictive check, simulations of taurine concentration obtained in WN and UN animals were found. The nutritional assessment revealed that 81% (n = 26) of the animals in the UN group developed moderate to severe undernutrition.

No statistical differences between basal taurine plasma concentration obtained in WN and UN animals were found (WN (50-97 (so 14-54) mg/l) and UN (48-86 (so 22-11)) mg/l (P > 0.05)). Taurine plasma concentration-time profiles obtained after IV and oral administration are shown in Fig. 1. The experimental data used in the model development were taurine plasma concentration v. time.

A Michaelis–Menten process was fit to identify the kinetics of distribution and elimination processes (disposition phase, steps 1 and 2). The empirical model revealed non-linear excretion phenomena, but failed to provide any relevant information. Taking into account that taurine is mainly excreted in urine with high variations, a saturable renal tubular secretion and reabsorption process was tested. The model with active renal excretion and reabsorption was chosen in this step. When a mechanistic approach was considered, using data from WN and UN animals (Step 3), the influence of nutritional status on Vms, Kms, Vmr and Kmr parameters was evaluated. This step showed that the active secretion process of taurine was decreased in undernutrition status; Vms was 10% lower in UN animals.

In the final step (Step 4), disposition parameters were fixed to those obtained in the previous steps and oral administration data of UN and WN animals were added. The absorption

Results

Table 2 shows mean values, standard deviation and 95% CI of serum albumin, total cholesterol and body weight at the beginning and the end of the adaptation period for WN and UN animals. The nutritional assessment according to serum albumin and body weight is also shown. There were no differences between body weight, serum albumin or total serum cholesterol before the adaptation period. However, at the end of the adaptation period statistical differences were found in body weight and serum albumin between WN and UN animals (P < 0.0001). As previously reported, the weight evolution of UN animals was best described by linear weight gain and a decline module characterised by exponential weight loss, where the weight loss rate constant is an exponential function of time. Total serum cholesterol showed a non-statistical decrease. The nutritional assessment revealed that 81% (n = 26) of the animals in the UN group developed moderate to severe undernutrition.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (SD)</th>
<th>95% CI</th>
<th>Mean (SD)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>232 (56)</td>
<td>180, 284</td>
<td>238 (58)</td>
<td>189, 287</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>34 (8)</td>
<td>26, 43</td>
<td>31 (7)</td>
<td>24, 38</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Total serum cholesterol (g/l)</td>
<td>1.35 (0.3)</td>
<td>1.0, 1.7</td>
<td>1.09 (0.2)</td>
<td>0.85, 1.34</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 2. Biochemical and biometric parameters and values obtained for classifying the degree of undernutrition (Mean values and standard deviations and 95% confidence intervals)
process is best described by passive diffusion kinetics. Oral bioavailability was also incorporated in the model as a function of the oral dose administered and nutritional status. In all cases, results were very similar to 1 (100% bioavailability).

Fig. 2 illustrates the schematic structure of the model and the corresponding equation (Equation (3)) that best defined the pharmacokinetic profile of taurine:

\[
\frac{dC(1)}{dt} = Q_0 + k_a C(3) - k_{12} C(1) + k_{21} C(2) - \frac{V_{ms} \cdot (R_{UN})^N C(1)}{K_{ms} + C(1)} + \frac{V_{mr}(4)}{K_{mr} + C(4)}
\]

where \(k_a\) is the oral absorption rate, \(Q_0\) the basal level of taurine, \(K_{12}\) and \(K_{21}\) the inter-compartmental distribution constants, \(V_{mr}\) and \(K_{mr}\) the reabsorption Michaelis–Menten constants, \(V_{ms}\) and \(K_{ms}\) the elimination Michaelis–Menten constants, \(F_{UN}\) the reduction of \(V_{ms}\) calculated in UN animals compared with WN animals. NUT = 0 in WN or 1 in UN.

Table 3 shows the estimated values for the pharmacokinetic parameters of the final model (covariance step aborted). Individual taurine plasma concentration values predicted with the selected model are also shown in Fig. 1 as a line. Individual and population predicted vs observed taurine plasma concentrations are plotted in Fig. 3. Weighted residuals (WRES) vs. time and absolute individual weighted residuals |IWRES| vs. individual
Malnutrition is associated with variations in drug absorption and drug disposition owing to changes in protein binding, hepatic metabolism and renal elimination(36,57). As a consequence, drug toxicity increases and the response to treatment is altered. In such a situation, conditionally essential nutrients, such as taurine, that are mainly provided by dietary intake may have altered body levels. However, only a few studies have, thus far, evaluated the influence of malnutrition on the pharmacokinetics of nutrients, such as taurine, in malnourished patients(38).

The present study was undertaken to determine the pre-clinical pharmacokinetic model of taurine after oral, as well as IV, administration and to investigate the influence of nutritional status on the pharmacokinetics of this amino acid. To detect possible non-linearity, three doses of the amino acid were administered. Such information is essential when a regimen for administration of this agent to patients is designed.

The empirical models in steps 1 and 2 were fit in order to determine the compartmental model suitable for taurine and to detect possible non-linearity in the disposition processes. Both steps revealed that the model that best fitted the data was a bicompartimental model with non-linear phenomena in the elimination process, which agrees with the literature, where it has been described that taurine transport undergoes an adaptive response to changes in taurine availability and body requirements(39).

Contrary to most amino acids, taurine is not metabolised and does not bind to protein but remains free in the intracellular water. Most amino acids are reabsorbed at rates of 98–99%. Reabsorption of taurine, however, may range from
0.5 to 99.5%, suggesting an adaptive regulation of transport in the kidney. In step 3, the effect of covariates, final body weight, final serum albumin, final serum cholesterol and degree of undernutrition in those parameters, was checked to detect the influence of nutritional status on the pharmacokinetic parameters. Linear, exponential and potential equations were explored. As these analyses failed, nutritional status was introduced in the fitting as a factor. The best fit was obtained with

Fig. 4. Taurine plasma concentrations. Results of the model exploration exercise (visual predictive check), in which total plasma concentration–time profiles of taurine were simulated 200 times. Experimental plasma concentration of taurine (-). Lines represent 5th, 50th and 95th percentiles. WN, well-nourished animals; UN, undernourished animals; IV, intravenous.
the bicompartimental model with non-linear elimination, depending on both the administered dose and nutritional status.

Given the small molecular size of taurine, a passive diffusion elimination process was first evaluated. However, during the mathematical modelling of data, the successful models showed that passive renal filtration was very low (<0.52 × 10^{-9} l/h per g), indicating that active elimination processes (saturable renal tubular secretion and reabsorption) are significantly more relevant than passive diffusion (P < 0.01). Thus, renal filtration was not incorporated in the final model. The model selected in step 3 incorporates saturable renal tubular secretion and reabsorption, thus being in agreement with previous findings. As an endogenous compound, its renal clearance is modulated according to body requirements determined by uptake and pathophysiological changes. It has been described that its elimination is because of a process sensitive to the presence of Na and Cl ions and that it is partially reabsorbed by the TauT transporter located in the proximal tubules.

In this scenario, after administration of a 10-mg dose, active tubular reabsorption would be saturated, which would encourage elimination, and clearance would be higher than that observed with the 1-mg dose. Similarly, with the 100-mg dose, active tubular secretion and tubular reabsorption processes could both be saturated, so that clearance would be lower than in the case of the 1-mg dose, both in WN and UN. The influence of nutritional status on Vms, Kms, Vmr and Kmr parameters was also evaluated in this step. The saturation of the secretion process will first occur in UN animals, which showed a 10% lower Vms than WN animals; therefore, elimination in UN animals would be lower than in WN animals. This change in clearance, which was statistically significant (P < 0.01), may not have clinical relevance in higher dietary supplementation but may be of relevance in patients with normal or low taurine intake (1–10 mg each meal or 3–30 mg/d) in rats equivalent to 6–60 mg/meal (or 18–120 mg/d) in humans.

In the final step, step 4, oral data from WN and UN animals were added. Results showed that the oral absorption of taurine can be better described by a passive diffusion model that is not altered by the nutritional status. The model selected to describe taurine absorption differs from other publications. Intestinal transporters for taurine (TauT) that have low capacity and high specificity have been described. The differences found may be owing to the range of doses administered. The selection of the doses administered in our study was made according to the taurine doses granted in enteral diets designed for human patients (equivalent to 1 and 10 mg in rats), whereas the higher dose (100 mg) was chosen owing to its negligible toxicity. Doses of 1 mg and 10 mg of taurine orally administered did not significantly increase the plasma levels of the amino acid from the basal levels, whereas a dose of 100 mg of taurine could (Fig. 1).

Data obtained from the 100-mg administration might not have been sufficient to characterise the non-linearity in the absorption process. Moreover, it cannot be ruled out that if the transporter has low capacity it can be saturated at all doses administered. Finally, it has been described that this transporter activity seems to have low capacity it can be saturated at all doses administered.

Conclusions

Data analysis showed linear absorption and distribution, and non-linear elimination processes for taurine, with active processes, renal secretion and reabsorption implied. Elimination of taurine was reduced in UN animals, suggesting that the secretion transporter was significantly modified in this group. The taurine absorption process at the usual range of doses behaves as a passive process that is not altered in undernutrition.

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The authors have no conflicts of interest that might be relevant to the content of this paper.

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