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Potato glycoalkaloids and adverse effects in humans: an ascending dose study

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Abstract

Glycoalkaloids in potatoes may induce gastro-intestinal and systemic effects, by cell membrane disruption and acetylcholinesterase inhibition, respectively. The present single dose study was designed to evaluate the toxicity and pharmacokinetics of orally administered potato glycoalkaloids (α-chaconine and α-solanine). It is the first published human volunteer study were pharmacokinetic data were obtained for more than 24 h post-dose. Subjects (2–3 per treatment) received one of the following six treatments: (1–3) solutions with total glycoalkaloid (TGA) doses of 0.30, 0.50 or 0.70 mg/kg body weight (BW), or (4–6) mashed potatoes with TGA doses of 0.95, 1.10 or 1.25 mg/kg BW. The mashed potatoes had a TGA concentration of nearly 200 mg/kg fresh weight (the presently recognised upper limit of safety). None of these treatments induced acute systemic effects. One subject who received the highest dose of TGA (1.25 mg/kg BW) became nauseous and started vomiting about 4 h post-dose, possibly due to local glycoalkaloid toxicity (although the dosis is lower than generally reported in the literature to cause gastro-intestinal disturbances). Most relevant, the clearance of glycoalkaloids usually takes more than 24 h, which implicates that the toxicants may accumulate in case of daily consumption.

Keywords: Glycoalkaloids; Chaconine; Solanine; Human; Pharmacokinetics; Potato; Public health

1. Introduction

Potatoes (*Solanum tuberosum*) contain glycoalkaloids (GAs), a class of natural toxicants. The two major GAs are α-chaconine and α-solanine (Fig. 1), comprising 95% of all GAs. Both are glycosylated (trisaccharide) derivatives of the aglycone solanidine, a steroid alkaloid. Produced in bioactive parts of the plant (flowers, young leaves, sprouts, and tubers), these substances protect the plant against fungi, insect pests and herbivores (Jadhav et al., 1981; Morris and Lee, 1984). GAs appear to have two toxic actions, one on cell membranes and another on acetylcholinesterase (Morris and Lee, 1984).

The toxicity on membranes leads to cell disruption, thought to be caused by the formation of destabilising complexes of the lipophilic moiety of the GAs with cholesterol in membranes (Keukens et al., 1992). Recent cell culture and experimental animal studies have shown that GAs may adversely affect intestinal permeability (Patel et al., 2002). As a consequence, for humans with for instance chronic inflammatory bowel disease, exposure to higher TGA concentrations might cause persistence

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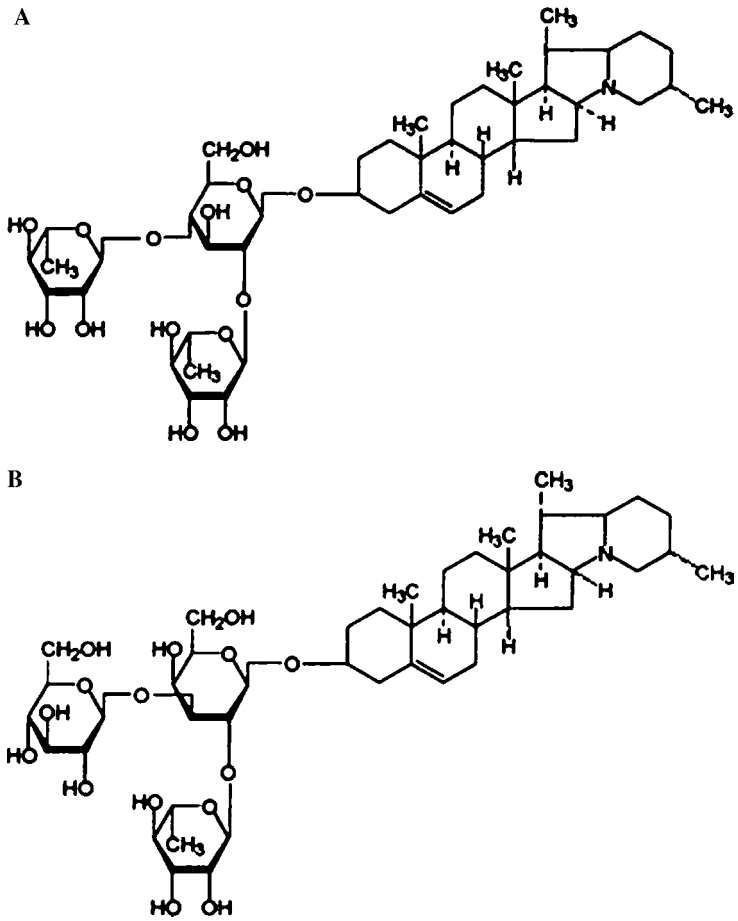

Fig. 1. Chemical structures of (A) α-chaconine and (B) α-solanine.

or aggravation of their illness. Potato glycoalkaloids have been estimated to be toxic in humans at doses greater than 2 mg of total GAs (TGA)/kg body weight (BW) (Morris and Lee, 1984); causing gastrointestinal disturbances like vomiting, diarrhoea, and abdominal pain. It is important to realise, that these kinds of poisoning are suspected to be underdiagnosed because the symptoms are similar to those of other common gastrointestinal ailments (Smith et al., 1996).

Potato GAs inhibit the enzyme acetylcholinesterase, thereby affecting the nervous system directly; with symptoms such as sweating, vomiting, diarrhoea, and bronchospasm. Severe poisoning may lead to serious adverse events, such as paralysis, respiratory insufficiency, cardiac failure, and coma. Cases of lethal poisoning have been reported at estimated doses greater than 3 mg TGA/kg BW (Morris and Lee, 1984). Furthermore, the inhibition of the enzyme may also alter the kinetics of drugs, e.g., neuromuscular blocking agents (Krasowski et al., 1997).

The total concentration of GAs (TGA) in consumption potatoes may vary considerably. Generally, the average amount of TGA in consumption potatoes is less than 100 mg/kg fresh weight (FW). But higher contents may occur. In the UK, a survey of 133 samples of commercial potatoes revealed average TGA levels between 90 and 175 mg/kg FW, while 2% even exceeded the recommended maximum level of 200 mg/kg FW (Davies and Blincow, 1984). And in Sweden, the potato variety Magnum Bonum (now banned) had even higher contents, up to 665 mg/kg FW (Hellenäs et al., 1995). Postharvest synthesis of GAs may increase the concentration of GAs, due to bad storage (higher temperatures, any light, and low humidity), mechanical damage, γ-radiation, and exposure to fungi. Chlorophyll synthesis usually turns these potatoes green, although there is no direct link between chlorophyll and glycoalkaloid synthesis (Edwards et al., 1998). Within potato tubers, GAs are concentrated mainly in the peel, with a range of 12–543 mg/kg FW (Friedman et al., 2003). Home peeling generally reduces glycoalkaloid intake considerably, 30% or more (Van Gelder, 1985). However, at high-TGA levels, the glycoalkaloids are not only concentrated in the outer layers but increase in the flesh of the tuber as well; reducing the effectiveness of peeling (Hellenäs et al., 1995). Note, that home cooking, frying, baking, and microwaving will not destroy GAs; they are fairly heat-stable. Their melting points, at which they may start decomposing, are in the range of 190–285 °C (NIEHS, 2003; The Merck Index, 2001).

Generally, 200 mg TGA/kg FW potatoes is accepted as the upper safety limit (Bömer and Mattis, 1924; Smith et al., 1996). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) considers a TGA content of less than 100 mg/kg potatoes FW of no concern (JECFA, 1993). Note, that these are potato-based recommendations. A no observed adverse effect level (NOAEL) and a tolerable daily intake level (TDI) have not been set yet. The presently available epidemiological and experimental data from human and laboratory animal studies are not sufficient to determine a realistic safe level of intake.

For several reasons it is important to gain further insight in glycoalkaloid toxicity. First, the potato is part of the regular diet for about a billion people world-wide. Second, the present TGA concentration limit in potatoes has economical consequences for potato breeders. New (and old) potato variants cannot be marketed if they contain TGA concentrations above 200 mg/kg. Third, because of industrial food handling. Potato chips (crisps), e.g., may contain high-TGA levels, up to 720 mg/kg (Sizer et al., 1980). And fourth, fundamental changes in production technology, using potatoes as inexpensive sources of high-quality intermediary products. For example, food colourings (with strong TGA attachment), such as anthocyanin (Rodriguez-Saona et al., 1999), may increase the daily intake of potato glycoalkaloids.

At present, there is a lack of potato glycoalkaloid toxicity data in humans (JECFA, 1993). And, extrapolation of present animal data would yield a safety limit below the present levels of exposure in humans. To gain more insight in the potential risks of potato GAs, we therefore performed a clinical trial to evaluate the acute toxicity and pharmacokinetics over several days of a single orally administered glycoalkaloid dose. Because of the limited information on toxicity in relation to the TGA dose in humans, this study was set up as an ascending dose pilot study (up to 1.25 mg TGA/kg BW).

2. Materials and methods

2.1. Study design

This open, ascending dose, randomised trial was carried out in accordance with the guidelines for good clinical practice. The ethics committee of the University Medical Centre Utrecht approved all procedures. All subjects provided a written informed consent. To standardise for stomach emptying, subjects were kept in supine position from 1 h before until 4 h after treatment. Each treatment started at 09:00 h and ended within half an hour. All subjects kept the dietary rules to consume no other products with GAs, from 72 h prior until study end. Furthermore, subjects had an overnight fast from 23:00 h the day before treatment.

2.2. Study population

The study was carried out at the University Medical Centre in Utrecht, The Netherlands. Adult volunteers, aged 18–45 years, were recruited through advertisements in the national press. The enrolled subjects (6 males, 8 females) were healthy, as determined by medical history, physical examination, and routine blood and urine tests. None of them used medication or antibiotics (from 2 weeks prior until study end) or had gastrointestinal complaints.

2.3. Intervention products

Subjects received one of the following six treatments: (1–3) in the form of solutions (ca 200 ml) with TGA doses of 0.30, 0.50 or 0.70 mg/kg BW, or (4–6) in the form of mashed potatoes with TGA doses of 0.95, 1.10 or 1.25 mg/kg BW. The glycoalkaloid low starting dose of 0.30 mg/kg BW was used to anticipate for possible adverse effects when administering solutions. The GAs for the solutions were obtained from Fluka (Buchs SG, Switzerland). The solutions contained 50% α-chaconine (formula $C_{45}H_{73}NO_{14}$, MW 852) and 50% α-solanine (formula $C_{45}H_{73}NO_{15}$, MW 868). A potato variety containing relatively high-amounts of TGA (199 mg/kg FW) was supplied by AVEBE (Veendam, The Netherlands). To keep the content of TGA constant during the study, the potatoes were processed by the Agrotechnical Research Institute (Wageningen, The Netherlands) to obtain potato flakes (by steam peeling, boiling, mashing, and drying). The potato flakes were canned under nitrogen atmosphere and stored at 4 °C until usage and checked for stability of TGA contents until the study was finalised. The mashed potato portions (containing 49% α-chaconine and 51% α-solanine) were prepared within an hour before administration by mixing the flakes with hot tap water (90 °C).

2.4. Outcome measures

Venous blood samples were taken at the following time points: −1, −1/2, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 32, 48, 56, 72, and 96 h from consumption start. Serum samples were obtained after complete precipitation of the cellular fraction (at room temperature), and then stored at −20 °C until analysis. In addition, blood pressure, and heart rate were monitored with a non-invasive automated blood pressure meter (Passport monitor Data-scope). Twelve-lead ECGs were obtained using a Hewlett–Packard cardiograph (type 4700-A). During the study any adverse events observed or reported were documented.

2.5. Analytical measurements and analytical quality control

Serum glycoalkaloid concentrations (α-chaconine and α-solanine) were determined by means of straight phase high-performance liquid chromatography (HPLC) with UV detection (detector TSP UV, length flowcell 10 mm, λ 201 nm). First, serum was cleaned by solid-phase extraction on a C2-SPE column (Isolute, 500 mg, 3 ml). The eluate was dried under N_2, redissolved in 200 μl acetonitrile–H_2O (1:1) and alkalinised slightly by adding 300 μl 0.11 M K_2HPO_4. The acquired 500 μl solution was cleaned further by injection on a HPLC column [10 cm × 3 mm; filled with Waters Spherisorb CN (cyanopropyl)] via an enrichment column (Prelute, 4.6 × 5.8 mm; filled with Hypersil ODS, 10 μ, 70 mg) mounted in place of the loop of a Rheodyne injection valve. Acetonitrile—9.8 mM K_2HPO_4 (84:16) was used as the mobile phase, with a flow of 1.0 ml/min. Second, the cleaned solution (collected by a Gilson 202 fraction collector) was evaporated under N_2, redissolved in 200 μl acetonitrile–H_2O (1:1) and alkalinised slightly by adding 300 μl of 58 mM K_2HPO_4. Finally, the solution to be analysed was injected on a HPLC column [15 cm × 2 mm; filled with Waters Spherisorb S3W silica (OH)], via an enrichment column (as mentioned earlier). Now using acetonitrile—26 mM K_2HPO_4 (80:20) as the mobile phase, with a flow of 0.2 ml/min. For calculation, samples were used consisting of blank serum fortified with a 50%/50% mixture of α-chaconine and α-solanine in a range from 0.5 to 50 ng/ml. The analysis was validated for LLQ (lower limit of quantification), linearity, within-day and between-day variation using blank serum (not containing any glycoalkaloid background levels). The LLQ for α-chaconine and α-solanine was 0.25 and 0.50 μg/L, respectively. The analyses demonstrated acceptable variation, within-day for α-chaconine 3–10% and for α-solanine 4–10%, and between-day for α-chaconine 6–8% and for α-solanine 8–9%, and was linear in the range of 0.5–50 ng/ml serum.

2.6. Data analysis

The above-described sample analyses provided individual data curves (serum concentration of GAs versus time) for each treatment. Pharmacokinetic parameters were calculated on the basis of the observed curves, using the software programme TopFit (version 2.0). The following individual kinetic parameter values were calculated: peak concentration level (C_{max}), time of the peak level (t_{max}), elimination half-life ($t_{1/2}$), the AUC (area under the curve) up to 24 h (AUC_{0-24}) and total ($AUC_{0-\infty}$). Descriptive statistics (range values) were used to present the data. Pearson correlation coefficients were calculated to quantify the relationship between dose and C_{max} and between dose and AUC. Additionally, linear regression analyses were used to predict the C_{max} or AUC value from the administered dose.

3. Results

Figs. 2A and B depict loglinear plots of the serum concentrations of α-chaconine and α-solanine with time, using the data of two different participants. One of them was given the highest TGA solution dose (A, 0.70 mg TGA/kg bw) and the other the highest mashed potato dose (B, 1.25 mg TGA/kg bw). For the TGA solution dose as well as the mashed potato dose, the serum concentrations of both α-chaconine and α-solanine increase steadily after consumption, reaching their peaks (C_{max}) after about 6 h. Thereafter, the serum concentrations of both GAs decrease gradually, but do not return to baseline within 24 h post-dose.

Table 1, summarises the results of the kinetic analysis of the serum concentration-time curves of both α-chaconine and α-solanine for six dose levels. The lowest three dose levels concern TGA solutions, while the highest three dose levels concern mashed potato portions. The

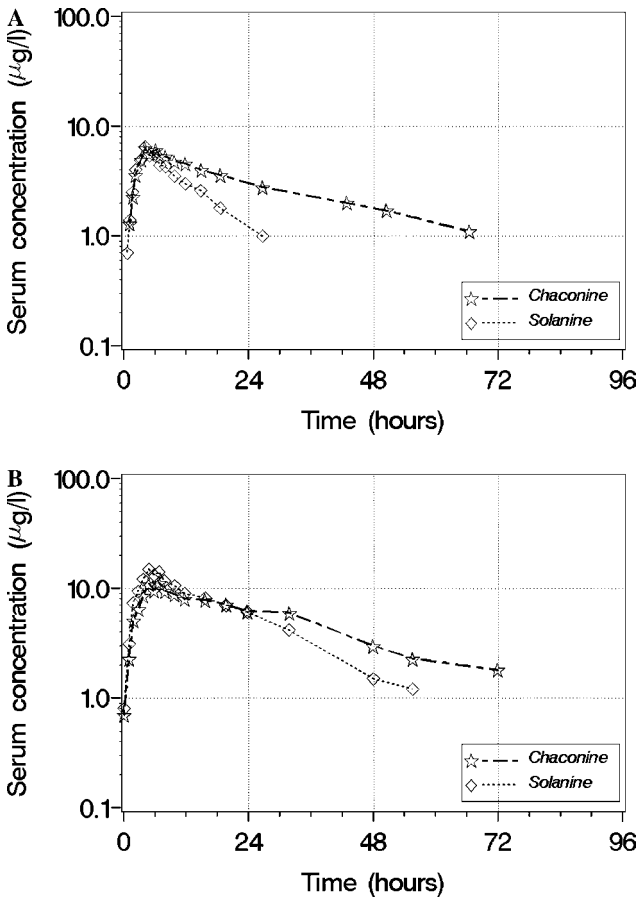

Fig. 2. Loglinear plots of the serum concentrations of α-chaconine and α-solanine with time, using the data of two different participants. One of them was given the highest TGA solution dose (A, 0.70 mg TGA/kg bw) and the other the highest mashed potato dose (B, 1.25 mg TGA/kg bw).

individual absolute TGA doses were calculated and found to range from 18.3 to 90.2 mg. For both α-chaconine and α-solanine, the C_{max} values seem to increase with increasing dose. A similar trend exists for AUC_{0-24} and $AUC_{0-\infty}$. Generally, the time of peak concentration (t_{max}) varies from 4 to 8 h. The half life values ($t_{1/2}$) for α-chaconine (range 27–84 h) were higher than the ones for α-solanine (range 5–42 h), both quite variable.

Fig. 3, for all dose levels, shows the intra-individual correlation between the C_{max} values of α-chaconine and α-solanine. The C_{max} values have a strong positive correlation, for the TGA solution doses (Pearson correlation coefficient 0.98, $p < 0.01$) as well as the mashed potato doses (Pearson correlation coefficient 0.97, $p < 0.01$). A similar trend (data not shown) was observed for the intra-individual correlation between the AUC_{0-24} values of α-chaconine and α-solanine. The intra-individual correlation for $AUC_{0-\infty}$ values was statistically significant for mashed potato doses only.

Figs. 4A and B, depict the peak concentrations (C_{max}) by absolute dose, for, respectively, α-chaconine (A) and α-solanine (B). A subject-specific letter (A–N) indicates each individual separately. Both graphs indicate that there exists a positive relation between absolute dose and C_{max}. The relationship between absolute dose and C_{max} value was quantified by fitting a regression line through the data: $C_{max} = +\beta_1 * \text{Dose}$. The linear regression lines were forced through the origin (all concentrations were corrected for baseline). C_{max} was significantly related with absolute dose, for α-chaconine as well as α-solanine,

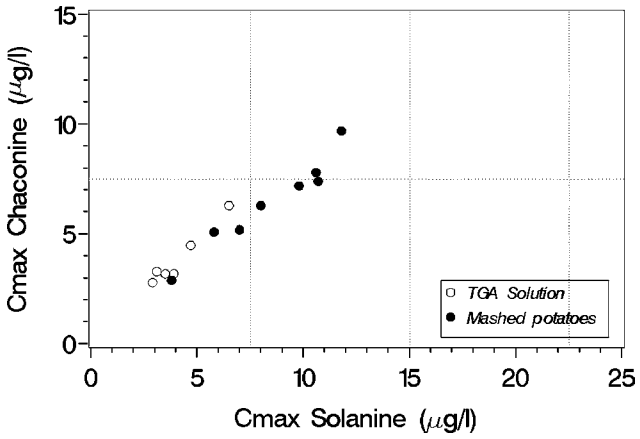

Fig. 3. Intra-individual correlation between the C_{max} values of α-chaconine and α-solanine, for the TGA solution doses (empty circles) and for the mashed potato doses (filled circles).

in both forms of administration. The regression analysis was repeated including all doses (from 0.30 to 1.25 mg TGA/kg body weight), now with an additional independent dichotomous variable (0/1) for the form of administration ($\beta_2 * \text{Matrix}$). The regression coefficient β_2 was found to be non-significant, for both α-chaconine and α-solanine. Overall, the data of this study suggest there is no saturation of the absorption over the used dose-range. A similar trend was observed (data not shown) regarding the relationship between absolute dose and AUC. Comparison of the arrangement of subject-specific letters in both graphs (A versus B) shows that the

Table 1
Pharmacokinetic parameters (ranges) for α-chaconine and α-solanine serum concentrations by test product and by TGA dose

	TGA dose (mg/kg BW)[a]					
	TGA solution			Mashed potatoes		
	0.30	0.50	0.70	0.95	1.10	1.25
TGA solution (mg/ml)	0.096	0.160	0.224			
Mashed potatoes (g)[b]				320–377	393–453	440–452
Number of subjects	2	2	2	3	3	2
Body weight (kg)	61–66	60–65	62–71	67–79	71–82	70–72
Absolute TGA dose (mg)	18.3–19.8	30.0–32.5	43.4–49.7	63.7–75.1	78.1–90.2	87.5–90.0
α-Chaconine						
C_{max} (μg/L)	2.8–3.2	3.2–4.5	3.3–6.3	5.2–7.4	2.9–7.8	6.3–9.7
t_{max} (h)	5–6	5–6	4–5	5–7	5–8	7–12
$t_{1/2}$ (h)	32–37	49–84	29–39	27–49	49–60	37–45
AUC_{0-24} (μg[a]h/L)[c]	41–48	54–60	53–106	89–112	45–112	98–143
$AUC_{0-\infty}$ (μg[a]h/L)[d]	117–130	148–242	128–227	237–345	168–316	299–419
α-Solanine						
C_{max} (μg/L)	2.9–3.9	3.5–4.7	3.1–6.5	7.0–10.7	3.8–10.6	8.0–11.8
t_{max} (h)	5–6	5–6	4–4	5–5	5–8	7–8
$t_{1/2}$ (h)	17–35	5–28	8–17	14–18	16–42	18–19
AUC_{0-24} (μg[a]h/L)	35–48	51–51	35–74	100–124	49–119	118–149
$AUC_{0-\infty}$ (μg[a]h/L)	84–89	57–110	50–86	164–193	111–200	204–256

[a] TGA = total glycoalkaloid = α-chaconine + α-solanine.
[b] TGA concentration 199 mg/kg potatoes (fresh weight), with α-chaconine/α-solanine ratio of 1.
[c] AUC, area under the curve, from point zero to 24 h.
[d] AUC from point zero to infinity.

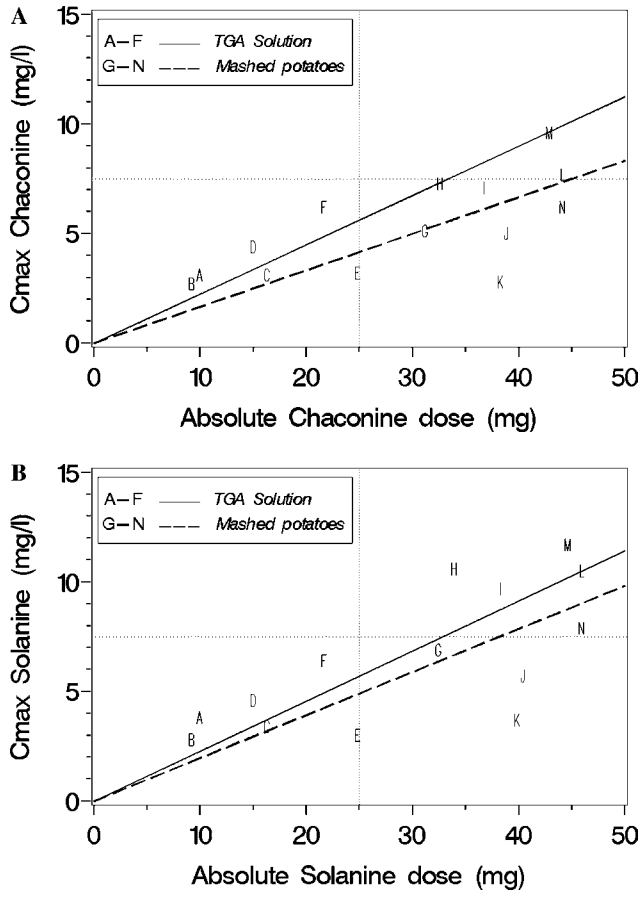

Fig. 4. Individual C_{max} values by absolute dose for (A) α-chaconine and (B) α-solanine, for both test administration forms (TGA solution and mashed potatoes). A subject-specific letter (A–N) indicates each individual separately. The solid and dashed lines represent the regression equation ($C_{max} = \beta_1 * \text{Dose}$) for TGA solutions and mashed potatoes administrations, respectively.

dispersion of C_{max} values is probably based on inter-individual differences, not on intra-individual variations.

Adverse events did occur in none of the treatments, except for the highest TGA concentration in mashed potatoes (1.25 mg/kg BW). One of two subjects in that group experienced effects. This subject became nauseous and vomited about 4 h after consumption of the mashed potatoes. The serum glycoalkaloid concentrations were comparable to those of the subject receiving a similar dose, whom did not experience any symptoms.

At TGA concentrations of up to 224 mg TGA/L in the administered solutions (highest absolute dose 49.7 mg) and 199 mg TGA/kg in the administered mashed potato meals (highest absolute dose 90.2 mg) none of the participants reported a bitter taste, usually associated with glycoalkaloids.

4. Discussion

In this study, the bioavailability of potato glycoalkaloids in humans is investigated, specifically because of the expected small margin between safe and hazardous levels of exposure to potato glycoalkaloids and the importance of potatoes in the human food chain. The study was tuned for common consumer conditions, using the original matrix (potatoes) with realistic consumer quantities. The study is, as far we know, the second published experimental study in humans that investigates the kinetics of potato GAs (α-chaconine and α-solanine) following the consumption of mashed potatoes and the first one that follows the kinetics of potato GAs for several days. The first experimental study, performed by Swedish investigators, was primarily designed to evaluate an analytical procedure for the determination of glycoalkaloid concentrations in serum (Hellenäs et al., 1992). The Swedish study was limited with regard to the number of investigated concentration-time points, up to 8 h post-dose, with one additional sample at 25 h post-dose. They used one TGA concentration only, 1 mg/kg BW (based on a α-chaconine/α-solanine ratio of 1.5). In the present study, the post-dose investigation time was extended to 96 h, with multiple concentration-time points in the elimination phase. Furthermore, different doses were used (up to 1.25 mg TGA/kg BW) to gain further insight in the relationship between the external dose and the kinetics of α-chaconine and α-solanine (based on a common α-chaconine/α-solanine ratio of 1).

The results of the two studies can be compared with regard to the height of the serum peak concentrations and with regard to the time it takes to reach them. At a comparable dose level, the heights of the serum peak concentrations were slightly lower for α-chaconine in the present study, and quite similar for α-solanine. Both studies revealed that the peak concentrations were reached after approximately 4–8 h. Both studies showed that none of the serum glycoalkaloid concentrations returned to baseline within 24 h post-dose. Furthermore, in the present study it was demonstrated that both α-chaconine and α-solanine had long half-lives, on average 44 and 21 h, respectively. This implies that daily consumption of potato products may cause accumulation of glycoalkaloids, which may consequentially lead to adverse health effects.

The present study yields additional information about the relationship between the administered dose and concentrations of potato glycoalkaloids in serum. Within the dose ranges used (of 0.30–0.70 mg TGA/kg body weight for the TGA solution doses and 0.95–1.25 mg TGA/kg body weight for the mashed potato doses), there is a clear and significant relationship between dose and C_{max} and between dose and AUC (especially AUC_{0-24}). Overall, the data suggest linearity in the relationship of dose with both C_{max} and AUC. Whether or not the linearity in the relationship continues for doses above 1.25 mg TGA/kg body weight needs to be confirmed in another study. The data further suggest that the intra-individual variation in C_{max} and AUC

are small while the inter-individual differences are relatively large. This means that some subjects may be more susceptible for adverse systemic effects (at higher doses) than others.

One of the participants given the highest dose (1.25 mg TGA/kg body weight) became nauseous and vomited about 4 h post-dose. Although this was a single observation, the Swedish study (using slightly lower dose levels of 1 mg TGA/kg body weight) reported similar effects as well, in one case accompanied by diarrhea. Cell wall disruption or inhibition of cholinesterase in the intestinal tract might very well be responsible for these symptoms. And, important to mention, these gastrointestinal effects may thus occur at relatively low levels of exposure, lower than 2 mg TGA/kg body weight as estimated by retrospective data (Morris and Lee, 1984). Potato glycoalkaloid related health effects are not frequently reported. It is however unclear whether or not there is serious underreporting, considering the fact that potato products are consumed (almost) daily and a lot of people experience periods of gastrointestinal disturbances. Presently, the analyses of α-chaconine and α-solanine are not available as a routine diagnostic tool.

From the results of the present study we conclude, that the administered single doses of up to 90.2 mg TGA (1.25 mg TGA/kg body weight) did not induce acute systemic effects. In only one subject, at the highest level of exposure (1.25 mg TGA/kg body weight), some local gastrointestinal effects were experienced by the volunteer, possibly due to local glycoalkaloid toxicity. The results furthermore show that the clearance of potato glycoalkaloids usually takes more than 24 h, thus these substances have the potential to accumulate in the body. As saturation of absorption was not observed for the administered dose-range, accumulation of GAs can be expected, especially after exposure to higher doses than used in this study. To establish an adequately based no observed adverse effect level (NOAEL) and an adverse effect level, additional studies are needed, including repeated dose investigations. In these studies, it is also necessary to further examine the inter-individual variability, because some individuals might be more susceptible to potato glycoalkaloid toxicity than others (e.g., patients with chronic inflammatory bowel diseases).

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