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INORGANIC COMPOUNDS

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Bismuth biokinetics and kidney histopathology after bismuth overdose in rats

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Abstract Bismuth induced nephrotoxicity has been reported to occur after acute overdoses of Bi-containing therapeutic drugs. We studied the development of bismuth induced nephropathy and bismuth biokinetics in rats. Bismuth nephropathy was induced in 33 young adult female Wistar rats weighing ca. 175 g by feeding them a single overdose of colloidal bismuth subcitrate containing 3.0 mmol Bi/kg at ($t = 0$). Control animals ($n = 7$) were fed the vehicle only. The animals were sacrificed after 1–48 h. Plasma creatinine increased from 51 ± 6 μmol/l at $t = 0$ to 550 ± 250 μmol/l after 48 h in the experimental group. The S3 segment of the proximal tubule showed epithelial cell vacuolation after 1 h and necrosis after 3 h. Cells of the S1/S2 segment demonstrated vacuolation after 6 h and necrosis after 12 h. Biokinetics of bismuth in blood could best be described with a one-compartment model characterized by an absorption half-life of 0.32 h and an elimination half-life of 16 h. The peak concentration of about 7.0 mg Bi/l was reached after 2 h. In conclusion, cells of the S3 segment of the proximal tubule necrotized first after an oral colloidal bismuth subcitrate overdose and biokinetics of Bi in blood was best described by a one-compartment model.

Key words Bismuth · Colloidal bismuth subcitrate · Nephrotoxicity · Nephropathy · Proximal tubule · Rat

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Introduction

Bismuth-containing therapeutic drugs, including colloidal bismuth subcitrate (CBS), are used to treat peptic ulcers and as part of a therapy to eradicate *Helicobacter pylori* in the stomach. Acute overdoses of these drugs have been reported to result in nephrotoxicity (Akpolat et al. 1996; Hudson and Mowat 1989; Huwez et al. 1992; Stevens et al. 1995; Taylor and Klenerman 1990; Urizar and Vernier 1966), but little is known of its pathogenesis. We therefore investigated the morphology and bismuth biokinetics of this nephropathy. In a previous experiment we found that in rats a single large oral dose of CBS containing 3.0 mmol Bi/kg body weight resulted in acute tubular necrosis within 48 h and in a significant rise in plasma creatinine levels as early as 6 h after administration. The induced renal damage healed spontaneously, as confirmed both morphologically and functionally, within 10 days. A CBS dose containing 1.5 mmol Bi/kg resulted in much less renal damage that healed more rapidly, whereas a CBS dose containing 0.75 mmol Bi/kg induced no detectable damage at all. In the highest dose group a significant correlation was found between plasma creatinine and the total amount of bismuth excreted in the first 6 h after CBS administration and the bismuth concentration in blood after 24 h. The present experiment examined the early development of bismuth-induced renal damage and on the biokinetics of bismuth in blood after a CBS overdose. The earliest point in time after which renal injury can be detected morphologically is of clinical relevance because treatment aimed at preventing damage must be performed before renal injury becomes clinically manifest.

Materials and methods

Animals

Inbred female Wistar rats were obtained from the breeding facilities of the Department of Pathology of Leiden University Medical

Center. The animals were housed under a 12/12 h light/dark cycle in climate-controlled chambers and had free access to tap water and rat chow (Hope Farms, Woerden, The Netherlands). The experiment was approved by the animal experiments committee of Leiden University. At the start of the experiment the animals were 11–12 weeks old and weighed between 129–201 g (177.0 ± 13.3 g).

Chemicals

CBS (tripotasium dicitratobismuthate) containing 35.4% (w/w) of the element bismuth was donated by Yamanouchi Europe (Leiderdorp, The Netherlands). Ultrapure water was prepared using a Milli-Q microfiltration device (Millipore corporation, Bedford, Mass., USA).

Experimental design

Forty rats were randomly divided into a treatment group of 33 animals and a control group of 7 animals using a randomization table. At $t = 0$ each animal in the treatment group was weighed and received by oral gavage a single dose of CBS, freshly dissolved in 0.5 ml saline, containing 3.0 mmol Bi (627 mg) per kilogram body weight. The dose administered was the lowest dose which induced severe renal damage in most animals (unpublished results). The animals in the control group received the saline vehicle only. From 18 h before until 6 h after administration the animals had free access to water only. Animals were sacrificed 1, 3, 6, 12, 24, or 48 h after administration to obtain the kidneys. At each time point five animals of the treatment group and one animal of the control group were sacrificed, except after 48 h when three animals of the treatment group and two animals of the control group were sacrificed. Urine of all surviving animals was collected in the periods of 0–6 h, 6–12 h, 12–24 h, and 24–48 h. Blood samples (0.5 ml) were collected just before sacrifice and, depending on the time of sacrifice, at one, two, or three of the following eight time points: 0.5, 1, 2, 3, 6, 12, or 24 h. After 0.5 h 15 blood samples were obtained, after 1 h 13, after 2 h 14, after 3 h 12, after 6 h 15, after 12 h 8, after 24 h 5, and after 48 h 3. Control samples of blood and 24-h urine were obtained 4 days before the start of the experiment from all animals.

Sampling and storage of blood, urine, and organs

Blood samples were drawn from the retro-orbital plexus with a Pasteur pipette under anesthesia with diethylether (Merck, Darmstadt, Germany). Heparin (Thromboliquine, Organon Teknica, Boxtel, The Netherlands) was added to the sample to prevent clotting. Samples of 100 µl whole blood were stored at −20 °C until the analysis of bismuth concentration. Plasma samples, obtained by centrifuging the remaining whole blood, were stored at −20 °C until the determination of creatinine and urea levels.

Urine was collected by placing the rats in thoroughly cleaned metabolic cages. Urinary samples were stored at −20 °C before and after centrifugation for 10 min at 1500 *g* until determination of bismuth, protein, and glucose concentrations.

Rats were killed by puncture of the abdominal aorta with a heparinized syringe under anesthesia with a mixture of ketamine, fluanison, fentanyl, and droperidol. Both kidneys were perfused with phosphate-buffered saline. The left kidney was removed and cut in half. One half was frozen in cold (−70 °C) methyl butane (Merck, Darmstadt, Germany) and stored at −80 °C until cryostat sections were made. The other half was stored in preweighed polystyrene tubes (Sarstedt, Nümbrecht, Germany) at −20 °C until bismuth determination. The right kidney was subjected to a second perfusion with 3.8% phosphate-buffered formaldehyde at pH 7.4 (Mallinckrodt Baker, Deventer, The Netherlands), then removed, cut in half, fixed with 3.8% phosphate-buffered formaldehyde for 24 h, transferred to 70% ethanol, and embedded in paraffin. Three-µm sections were stained according to the periodic acid–Schiff (PAS) procedure.

Panleukocyte staining

To evaluate the influx of inflammatory cells panleukocyte staining was performed on 4-µm cryostat sections with the OX1 mouse IgG1 monoclonal antibody directed against rat CD45 (Leukocyte Common Antigen; PharMingen, Hamburg, Germany). The StreptABComplex/HRP system (Dako, Glostrup, Denmark) in combination with the chromogen diaminobenzidine HCl (Sigma, St. Louis, Mo., USA) was used according to the instructions of the manufacturer to demonstrate OX1 antibodies in the tissue section. The number of $CD45^+$ cells was counted using a ×10 ocular containing a grid of 10×10 squares and a ×25 objective. The number of $CD45^+$ cells visible within the grid (the observation field) was counted at three different areas in the cortex and at three different areas in the corticomedullary boundary zone. Sections incubated with the second antibody only served as negative controls and gave a negative result in each case.

Analysis of blood and tissue samples

The bismuth contents of whole blood and kidneys were determined by electrothermal furnace atomic absorption spectrometry using platinum as a matrix modifier (Slikkerveer et al. 1991, 1993). The detection limits were 10 µg/l for 100 µl blood and 0.07 µg/g for 0.6 g kidney. The urinary bismuth content was determined by flow injection atomic absorption spectrometry with a detection limit of 1 µg/l (Price 1979).

Urinary glucose and protein levels and plasma creatinine and plasma urea were measured with a Hitachi 747 automatic analyzer (Hitachi, Japan) using standard clinical chemistry procedures.

Statistical analysis

All data were expressed as means ± SD. A statistical analysis was carried out using SPSS 7.5.2 (SPSS, Chicago, Ill., USA). Data obtained from animals that died not according to the schedule (i.e., from five animals in the experimental group) were excluded from the statistical analysis and the figures. For statistical analysis, all values below the detection limit were replaced by the detection limit itself. Means of parameters with a normal distribution were compared by paired or unpaired Student's *t* test. The Kruskal–Wallis one-way analysis of variance and the Mann–Whitney *U* test were used for those parameters lacking a normal distribution. To compare the number of $CD45^+$ cells a one-way analysis of variance followed by a least squares difference test was used. A *P* value lower than 0.05 was considered to indicate statistical significance.

Bismuth biokinetics

Individually determined bismuth concentrations in blood at nine time points (before the start of the experiment and 0.5, 1, 2, 3, 6, 12, 24, and 48 h after administration) were used for population kinetic analysis. Between 2 and 5 blood samples were taken from each animal, leading to 3–16 samples at each time point from the entire group. The number of samples per animal and per time point depended on the timing of the sacrifices.

The analysis was performed with the NONMEM software program (version V, NONMEM Project Group, University of California, San Francisco; Sheiner and Ludden 1992) using a one-compartment model with first-order absorption, assuming instantaneous absorption (no lag time) and a log-normal distribution of the biokinetic parameters. The residual error was assumed to be normally distributed, with a constant variation coefficient.

The actual bismuth concentration in blood was used as input for the population biokinetic model. An optimal fit between measured and predicted bismuth in blood values was selected. The obtained θ values and their distribution describing the population biokinetics and the actual concentrations in the individual animals were then used to calculate individual Bayesian predicted values of

concentration, clearance, volume of distribution, and absorption constant (K_a). Using these individual predicted values, the individual half-life ($t_{1/2}$), maximum concentration in blood (C_{max}) and area under the curve (AUC) were calculated. Pearson's correlation coefficients were computed to detect correlations between these parameters in relation to plasma creatinine levels after 12 h. The plasma creatinine after 12 h for each individual animal was estimated by introducing creatinine concentrations measured before the experiment and between 1 and 24 h in a linear regression model.

Results

Kidney function parameters

Five of the 33 animals in the experimental group that received a nephrotoxic CBS dose containing 3.0 mmol Bi/kg, died before they could be sacrificed. The results obtained from these animals were excluded from the statistical analysis and from the figures. Three animals died within 1 h of CBS administration, during the narcosis needed for the collection of the first blood sample after the administration of CBS. The two other animals died approximately 24 and 48 h after administration of the dose.

Plasma creatinine (Fig. 1A) and plasma urea (not shown) increased over the entire experimental period of 48 h. The increase was initially linear, but after 24 h, its rate declined.

Some of the animals in the experimental group became anuric after CBS administration. Six of 18 animals did not produce urine during 0–6 h, 9 of 13 during 6–12 h, and 5 of 8 during 12–24 h. Animals in the control group never became anuric. Mean urinary volumes of nonanuric animals in the experimental group differed significantly from those of the control group for 6–12 h (1.5 ± 0.4 vs. 3.5 ± 0.9 ml, $P = 0.005$). Glucosuria (Fig. 1B) and proteinuria (not shown) occurred only in the experimental group.

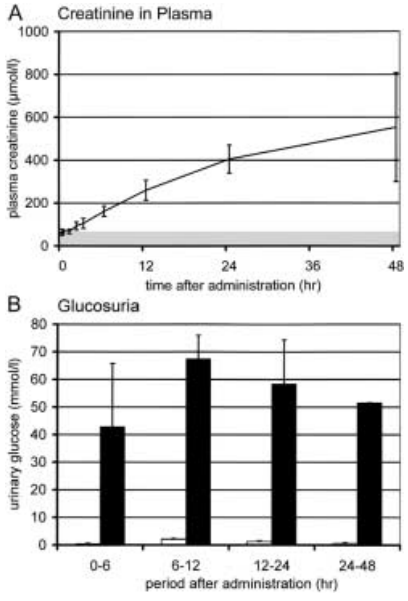

Fig. 1A, B Kidney function parameters over time. Creatinine in plasma (**A**) and glucosuria (**B**). *Gray rectangle* (**A**) mean plasma creatinine level of the control group (51.40 µmol/l) +2 SD (2×4.64). *Open bars* (**B**) means +SD of glucosuria values of the control group; *black bars* (**B**) means +SD of the animals which received a single oral dose of CBS containing 3.0 mmol Bi/kg at $t = 0$

Histology

Histological examination of the kidneys revealed cytoplasmic vacuolation of tubular cells at the corticomedullary boundary 1 h after CBS administration (Fig. 2B). After 3 h tubular necrosis had developed at this location (Fig. 2C). After 6 h cytoplasmic vacuolation occurred in tubular cells in the cortex. After 12 h necrotic tubules appeared in both the cortex and the corticomedullary boundary zone. Cortical tubular necrosis was always accompanied by necrosis of the corticomedullary boundary zone. The glomeruli remained normal at all time points. An increase in PAS-positive grains in the tubular cytoplasm was seen as early as 6 h after administration. The number of interstitial leukocytes, demonstrated by the anti-CD45 antibody, did not change before 48 h after CBS administration. In the control group 15.1 ± 3.4 $CD45^+$ cells per observation field were counted in the cortex. In the treatment group between 11.3 ± 2.4 and 18.9 ± 5.9 $CD45^+$ cells per observation field were observed. Neither figure differed significantly from the $t = 0$ value, by least squares difference test. In the corticomedullary boundary zone 16.1 ± 2.3 $CD45^+$ cells per observation field were found in the control group. In the treatment group the number of $CD45^+$ cells per observation field in the corticomedullary boundary zone varied from 7.5 ± 2.0 after 12 h to 32.0 ± 8.2 after 48 h. Only the latter value differed significantly from control.

Bismuth analysis

The CBS administration at $t = 0$ resulted in detectable bismuth concentrations in blood after 0.5 h. Before reaching its highest value 2 h after administration, the blood bismuth level first decreased significantly from 0.5 to 1 h (Fig. 3A; Student's t test, $P = 0.034$ with $n = 5$ for 0.5–1 h and $P = 0.011$ with $n = 4$ for 1–2 h). The number of animals available for the statistical test varied because blood samples only from animals sampled at both time points could be used. All urine samples taken from animals belonging to the control group or before CBS administration contained less than 1 µg bismuth. The majority of the urinary bismuth excretion took place within 6 h of CBS administration (Fig. 3B). The bismuth concentration in the kidneys was highest after 48 h and decreased thereafter, although much slower than bismuth concentrations in blood and in urine (Fig. 3C).

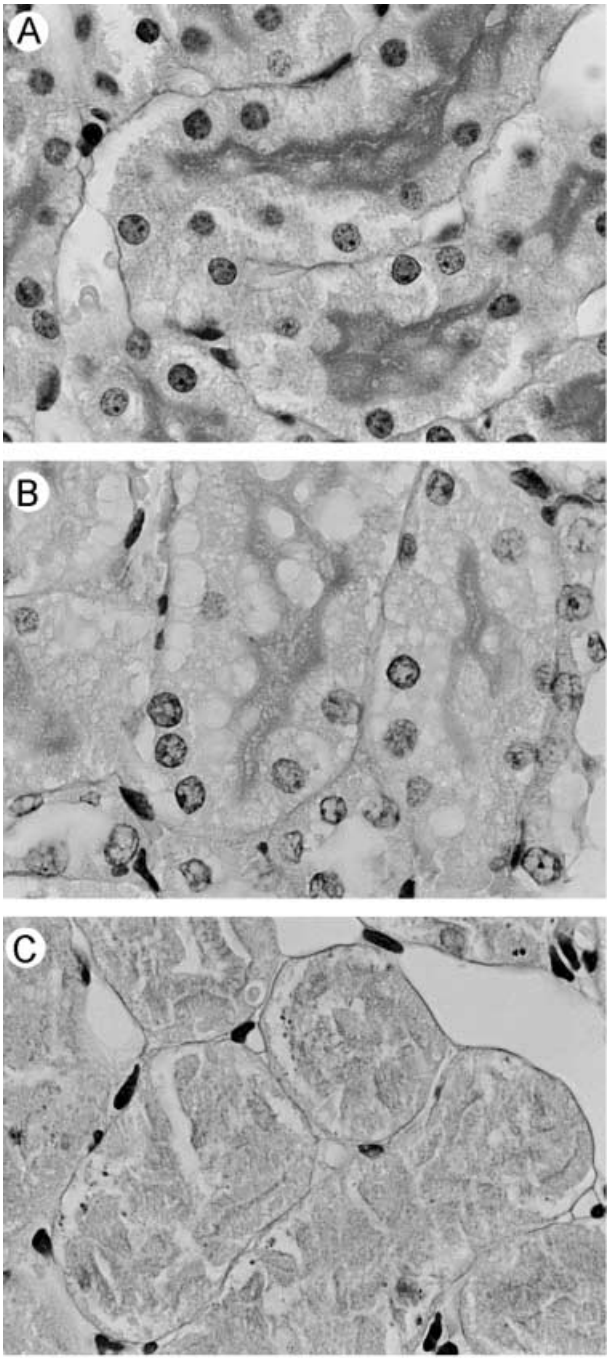

Fig. 2A–C Changes in kidney morphology after administration of an oral CBS dose containing 3.0 mmol Bi/kg. **A** S3 segments of the proximal tubule of an animal in the control group. **B** S3 segments 1 h after CBS administration. **C** S3 segments 3 h after CBS administration. Note that vacuolation of the tubular epithelial cells was present 1 h after CBS administration whereas tubular necrosis of the S3 segment was seen for the first time 3 h after administration. Kidney sections, 3 μm thick, paraffin embedded, PAS stained, ×600

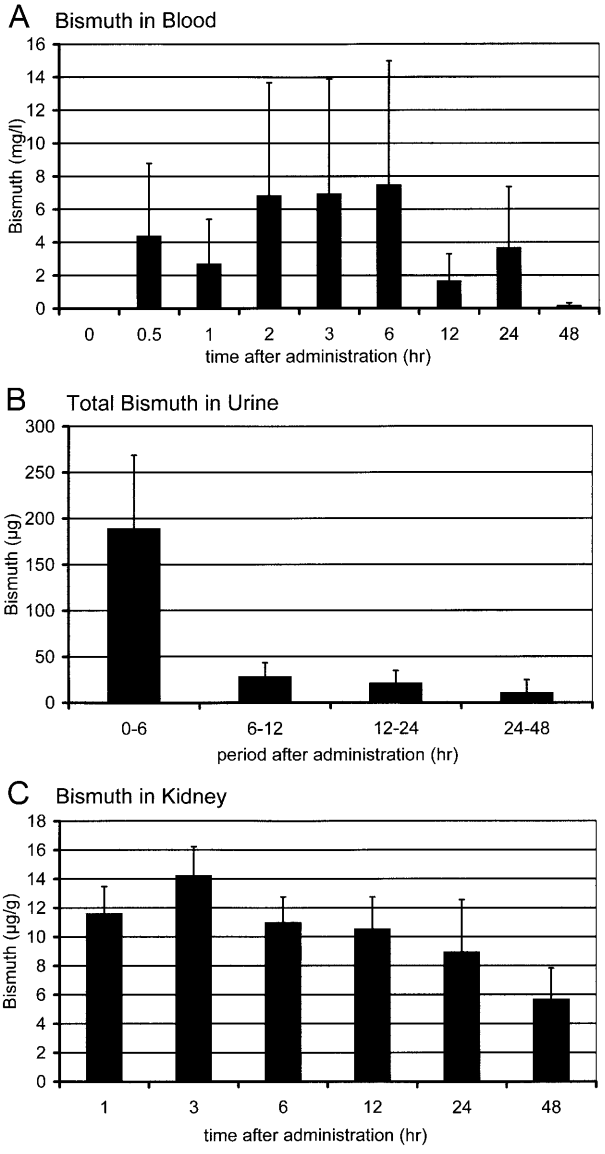

Fig. 3 Bismuth concentrations in blood (**A**), urine (**B**), and kidneys (**C**) over time. *Bars* mean ± SD of all animals producing urine after a single oral dose of CBS containing 3.0 mmol Bi/kg. The kidneys were perfused with phosphate-buffered saline before removal from the body

Bismuth biokinetics

The blood bismuth levels of the individual animals were used to compute a biokinetic model describing the behavior of bismuth in the body after a single oral CBS overdose. The population analysis (Table 1) showed a rapid absorption with an absorption rate constant of 2.14 h^{-1}, which corresponds to an absorption half-life of 0.32 h. Elimination was much slower. Typical values of 2.28 l h^{-1} kg^{-1} for apparent clearance and 65.7 l kg^{-1} for apparent volume of distribution were found, corresponding to an elimination half-life of 16 h (Fig. 4).

Two types of variation were calculated. The precision of the typical value indicates the precision of the population estimate. The variation indicates the variation in the parameter in the "general" population as calculated by the model. The best fit between the measured and the predicted concentrations of bismuth in blood with the lowest residual error (56.7%) was shown by a one-

Table 1 Population values describing a one-compartment biokinetic model for bismuth in blood after a single oral dose of CBS containing 3.0 mmol Bi/kg in female Wistar rats while inducing nephropathy

	Typical value for the population	Precision (SD) of the typical value	Variation (%) in the population
Apparent clearance ($l\ h^{-1}\ kg^{-1}$)	2.28	0.8	103
Apparent volume of distribution ($l\ kg^{-1}$)	65.7	29.4	301
Apparent K_a (h^{-1})	2.14	0.321	38

compartment model. At later time points the model fitted less well than at earlier time points, which may be explained by the decreasing number of animals available for blood sampling. The correlation ($r = 0.9799$), however, between the actual concentration in the blood and the predicted value was acceptable (Fig. 5). The best individual fits were obtained for animals with a wide range of sample times.

No correlations were found between plasma creatinine after 12 h and the computed biokinetic parameters AUC, C_{max}, and $t_{1/2}$. The respective Pearson's correlation coefficients were 0.186, −0.206, and 0.487.

Discussion

This experiment was designed to determine the development of renal injury over time and the biokinetics of bismuth after a large single CBS overdose.

Kidney function parameters and histology

Plasma creatinine concentrations increased at a constant rate after 1 h (Fig. 1A), indicating that all the damage to the renal clearance function is induced during the 1st h after CBS administration.

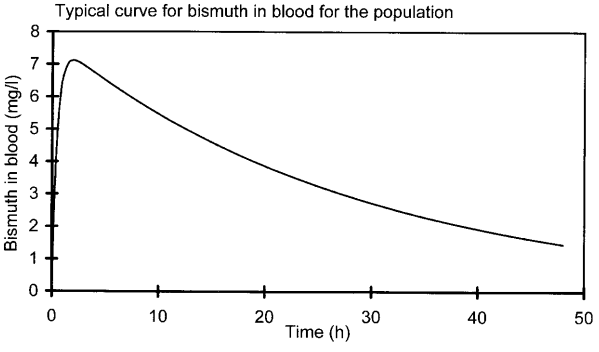

Fig. 4 Typical curve for bismuth concentrations in blood over time by means of a population approach after a single oral dose of CBS containing 3.0 mmol Bi/kg in female Wistar rats while inducing nephropathy

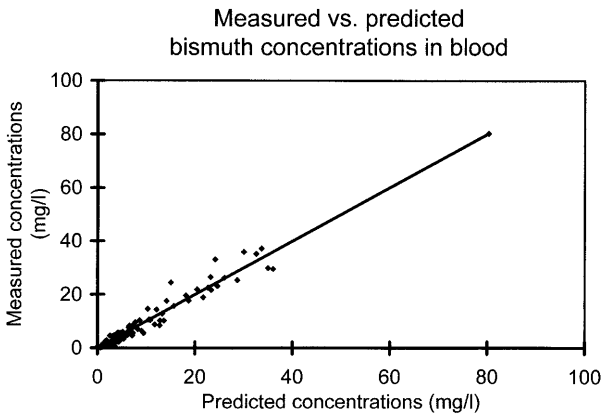

Fig. 5 Plot of actual bismuth concentrations in blood versus predicted concentrations ($r = 0.9799$)

The damaged tubules in the corticomedullary boundary zone (Fig. 2) were identified as S3 segments of the proximal tubule in a previous experiment based on their anatomical location, their characteristic large brush borders, and the absence of Tamm-Horsefall protein (Leussink et al. 1997). The S3 segment seemed most susceptible to bismuth-induced damage because it necrotized before 3 h after administration. Necrosis also occurred in the S1/S2 segment of the proximal tubule, located in the cortex, but only between 6 and 12 h after administration. This may indicate less sensitivity for bismuth of the epithelial cells in the S1/S2 segment than of those in the S3 segment. The tubular damage found in the present experiment was located at the same site as the vacuolation and atrophy of the tubular cells that were observed in female Wistar rats 3 days after ceasing repetitive subcutaneous injections with bismuth chloride (14.36 μmol Bi/kg) over the preceding 7 days (Szymanska et al. 1993).

Because the number of necrotic tubules increased between 3 and 12 h, and the rate at which the plasma creatinine rose remained constant, we conclude that bismuth-induced necrosis of proximal tubular cells is preceded by a reduction in renal function.

It seems unlikely that leukocytes are involved in the pathogenesis of bismuth nephropathy, as is the case in cisplatin-induced renal damage (Kelly et al. 1999) because the number of leukocytes did not increase significantly within 48 h after CBS administration. Results obtained in a previous experiment showed an increasing number of leukocytes after 48 h (unpublished observations), suggesting that leukocytes play a role in the recovery phase.

Bismuth analysis and biokinetics

Blood bismuth levels of the experimental group behaved in an unexpected way. They were significantly lower

after 1 h than after 0.5 or 2 h (Fig. 3A). This may result from the gradual induction of kidney damage during the absorption of bismuth from the intestine. Apparently, equilibrium between bismuth uptake in the blood and bismuth elimination from the blood is reached at two different points in time after administration of CBS. The first time point occurs around 0.5 h, as seen in humans after a single therapeutic CBS dose (Hespe et al. 1988). The blood bismuth level decreases afterwards, indicating that the elimination of bismuth from the blood temporarily supersedes its uptake. After about 1 h, when the equilibrium is reached for the second time, the balance between uptake and elimination is reversed, indicating that the gradually induced renal damage diminishes the renal clearance of bismuth and results in increasing blood bismuth levels.

The pharmacokinetic model showed a reasonable fit between measured and predicted blood bismuth levels, within the limited possibilities for blood sampling in the current study design. The number of samples was limited because the number of animals decreased as the experiment continued, and because only five blood samples could be obtained as a maximum from each animal. The one-compartment model is probably too simple, but provided the best fit. The bismuth-induced reduction in renal clearance could not be fitted but is likely to be responsible for at least part of the residual error observed. Additionally, the high variability in bismuth concentrations in blood may further explain the observed residual error.

The C_{max} in the general population curve of bismuth in blood was reached approximately 2 h after dose administration. In humans the C_{max} is reached 30 min after the intake of a single therapeutic CBS dose (Lacey et al. 1994; Hespe et al. 1988). The disposition of bismuth from the blood in rats after a nonnephrotoxic CBS dose is characterized by three elimination half-lives of 10, 36, and 295 h (Dresow et al. 1991). Since elimination times longer than 1 day cannot be detected in an experiment lasting only 48 h, the data from this experiment were best described using a one-compartment model with an elimination half-life of 16 h. The bismuth-induced kidney damage is probably responsible for this prolonged half-life as the reuptake of bismuth from the intestine after biliary excretion is limited. Biliary excretion plays a minor role in the elimination of bismuth from the body (Gregus et al. 1998).

Correlations between individual bismuth biokinetic parameters and renal function

For each animal the C_{max}, $t_{1/2}$, and AUC values of bismuth in blood were calculated by fitting the bismuth in blood concentrations of the particular animal into the general biokinetic model for the population. None of the calculated biokinetic parameters were correlated with creatinine in plasma after 12 h. A previous experiment had shown the creatinine in plasma after 48 h is accurately ($r^2 = 0.863$) predicted by a model using total bismuth in urine during 0–6 h and bismuth in blood after 24 h (unpublished results). This discrepancy has a number of possible explanations. Most importantly, in the current experiment the correlation was calculated between two indirectly calculated parameters. Additionally, the range of plasma creatinine values after 12 h was much smaller in the present study (260 ± 46 μmol/l) than plasma creatinine values after 48 h in the previous experiment (355 ± 170 μmol/l; unpublished results). In summary, the correlation observed in the earlier experiment between individual bismuth biokinetic parameters and renal function could not be shown in this experiment.

Clinical implications

The present studies lead to the conclusion that bismuth induces renal damage in a fast and direct way in a two-step process. The necrosis of the epithelial cells of the S3 segment of the proximal tubule occurs as early as 3 h after CBS administration and is followed by a similar event in the S1/S2 segment between 3 and 9 h later. On the assumption that the response to bismuth intoxication in humans is comparable to that in rats, treatment of a patient after a CBS overdose should start as soon as possible to prevent the early damage to the S3 segment. However, treatment at a later time point may be useful to prevent or diminish damage to the S1/S2 segment. Gastric lavage and chelation of bismuth in blood and tissues with *meso*-2,3-dimercaptosuccinic acid or D,L-2,3-dimercaptopropane-1-sulfonic acid may be used as therapy (Slikkerveer et al. 1992, 1998). The two-step injury model explains why some patients present to physicians as late as 10 days after a CBS overdose. In these cases only the S3 segment might be damaged (Hudson and Mowat 1989).

Conclusion

Wistar rats develop tubular necrosis in the S3 segment of the proximal tubule between 1 and 3 h after administration of an oral CBS overdose containing 3.0 mmol Bi/kg. After 12 h necrotic cells are also present in the S1/S2 segment. The calculated curve for bismuth in the blood among the general population is characterized by a peak of 7.0 mg Bi/l 2 h after administration and an elimination a half-life of Bi from blood of 16 h. If the conclusions of the present experiment can be extrapolated to humans, treatment of bismuth-induced nephropathy aimed at preventing renal damage must be performed within 3 h after the intake of the CBS overdose.

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manuscript. The experiments reported in this article comply with current Dutch law.

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