Comparison of enhanced elimination of bismuth in humans after treatment with 
meso-2,3-dimercaptosuccinic acid and 
D,L-2,3-dimercaptopropane-1-sulfonic acid

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Two groups of 12 human volunteers, who had been treated with colloidal bismuth subcitrate, because of Helicobacter pylori-associated gastritis, participated in the study. The patients received a single dose of meso-2,3-dimercaptosuccinic acid (DMSA) or D,L-2,3-dimercaptopropane-1-sulfonic acid (DMPS) at a dose of 30 mg kg⁻¹ in a randomized single blind study. In contrast to DMPS, increasing concentrations of bismuth in blood were observed during the first 4 h after intake of DMSA. In urine, both chelators induced a 50-fold increase in urinary bismuth excretion compared with the control urines. The treatment was well tolerated. The results indicate that both DMSA and DMPS effectively increase the elimination of bismuth in human urine. Consequently, both chelators may be of benefit in the treatment of patients with bismuth intoxication.

Keywords: Bismuth, meso-2,3-dimercaptosuccinic acid; D,L-2,3-dimercaptopropane-1-sulfonic acid; chelation, humans

Bismuth compounds are used in a wide range of gastrointestinal complaints, with special emphasis on the treatment of peptic ulcer disease and Helicobacter pylori infection. Bismuth intoxication is a rare but well known phenomenon. The metal has been known to cause nephro- or neurotoxicity dependent on many factors such as dose and type of bismuth compound.1 Animal studies showed that treatment of mice with acute bismuth intoxication with diithiol group containing chelators was effective in preventing mortality.2 A study in bismuth-loaded rats has shown that diithiol group containing chelators increased bismuth elimination in urine and reduced the bismuth body load significantly.3 Several case histories have been published4-6 on the use of chelators in the treatment of bismuth intoxication, but a controlled experiment in humans is only available for D-penicillamine.6

This study was performed to confirm the potential of diithiol chelators in the treatment of human bismuth intoxication. An overdose with bismuth-containing drugs is rare and it is known that small amounts of bismuth are left in the body for about 3 months after a normal treatment course with colloidal bismuth subcitrate (CBS). Therefore, the study was performed in patients who just had finished such a course of CBS. Based on the in vivo results in rats and clinical feasibility, two diithiol chelators were selected: meso-2,3-dimercaptosuccinic acid (DMSA) and D,L-2,3-dimercaptopropane-1-sulfonic acid (DMPS).

Study design
A group of 24 volunteer patients (age 26–65 years; mean 43 years) who had been treated with CBS (480 mg d⁻¹) for 28 d for Helicobacter pylori-associated gastritis received a single dose of DMSA or DMPS (30 mg kg⁻¹) in a randomized single blind study (n = 12). Subjects received the medication in gelatine capsules of 300 mg each. The study was performed between 7 and 14 d after the last day of treatment with CBS, because the steep decline in bismuth elimination in the urine directly after the end of treatment might have concealed an increase in bismuth elimination.

Before the administration of the chelator and 30, 60, 120 and 240 min thereafter, blood samples were collected. Urine was collected over 24 h before the chelator was given and 0–4, 4–8 and 8–24 h after administration. Bismuth in blood was determined by electrothermal atomic absorption spectrometry7 and bismuth in urine was determined with an FIAS-200 system and a Model 5100 AAS instrument with hydride formation.8

Volunteers were clinically observed for 4 h and adverse events occurring in the first 24 h were scored by questionnaire. Ethical approval for the study was granted by the hospital ethical committee and written informed consent from each volunteer patient was obtained.

Data analysis
The results are presented as means ± SEM. Bismuth concentrations in urine are expressed per μmole of creatinine (μg μmol⁻¹). The effects of the chelators on the bismuth concentration were analysed by repeated measures ANOVA (MANOVA) with paired Student’s t-tests for the detection of contrasts. Confidence limits of 95% were used.

Results
Before treatment with the chelators, no differences were present in bismuth concentrations in blood and urine between the groups. Blood levels of bismuth increased moderately after DMSA treatment. A small but significant decline (MANOVA, p = 0.002) in bismuth concentrations in blood was seen after intake of DMPS (Table 1). After 120 and 240 min blood levels of bismuth were significantly higher after treatment with DMSA (Student’s t-test, p = 0.018).

In urine, both chelators induced a 50-fold increase in urinary bismuth excretion compared with the control urines (Fig. 1). The highest amounts of bismuth were excreted in the first 4 h.
after ingestion of the chelators. A total amount of 2819 (± 268) μg of bismuth was excreted in 24 h after treatment with DMSA and 2700 (± 322) μg after treatment with DMPS. No significant differences in bismuth excretion were seen between the two chelators (MANOVA).

In 7 of the 24 patients minor side effects were observed such as transient diarrhoea, headache and nausea. The treatment was generally well tolerated.

Discussion
The present study indicates that both DMSA and DMPS effectively increase the elimination of bismuth in human urine. Consequently, both chelators may be of benefit in the treatment of patients with bismuth intoxication. Although differences in intestinal absorption between the two chelators have been reported,9 no significant differences with regard to the efficacy of urinary excretion of bismuth have been found.

In contrast to DMPS, increasing concentrations of bismuth in blood were observed during the first 4 h after intake of DMSA. This may be attributed to redistribution of especially the Bi–DMSA complex from tissue deposits to the vascular compartment. The increase in the blood concentrations of bismuth after treatment with DMSA is limited and causes no concern with respect to safety.

Given the dose (30 mg kg⁻¹) used in this single dose study, the study medication was remarkably well tolerated. This is in line with earlier reports from clinical experience that side effects are usually mild.9–11 The effect of both chelators on essential metals, such as Cu and Zn, is relevant to further evaluation of the clinical safety and applicability of these chelators. DMPS has been known to increase Cu and Zn elimination in humans, whereas DMSA only has minor effects on the elimination of Cu in urine and Zn in plasma.9,12,13 Nevertheless, this study has confirmed the previous indications that dithiol chelators are effective in the treatment of human bismuth intoxication.

Table 1 Concentrations of bismuth in blood (μg l⁻¹) 0–4 h after oral intake of 30 mg kg⁻¹ of DMSA or DMPS by human volunteers after a course of CBS (mean ± SEM; n = 12).

<table>
<thead>
<tr>
<th>Time after intake/min</th>
<th>DMSA</th>
<th>DMPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  30 60 120 240</td>
<td></td>
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<tr>
<td>Chelator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSA</td>
<td>15.8 ± 2.5 17.4 ± 3.3 21.2 ± 2.2 25.8 ± 3.0 33.4 ± 4.1</td>
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</tr>
<tr>
<td>DMPS</td>
<td>13.9 ± 1.2 16.2 ± 2.6 16.2 ± 1.5 15.9 ± 2.4 15.5 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1 Bismuth concentrations in urine after oral intake of DMSA or DMPS (30 mg kg⁻¹) by human volunteers (mean ± SEM; n = 12).

References