Two cases of acute toluene intoxication

J Meulenbelt, G de Groot, T J F Savelkoul

Abstract
Two patients exposed to high concentrations of toluene in air (> 7000 mg/m³) were found at the bottom of a small swimming pool under construction. Their symptoms were stupfaction, paresis, and amnesia. Patient A had been exposed for three hours and patient B for two hours. Ninety minutes after the exposure, the toluene blood concentration in patient A was 4·1 mg/l and in patient B 2·2 mg/l. Urinary ortho-cresol secretion was shown to be a good index of exposure to toluene. After high level exposure, urinary meta-cresol excretion may also be used to monitor toluene exposure.

Toluene is a widely used solvent and occupational exposure is common. A particular type of intoxication is caused by glue sniffing which, in some industrialised countries, has become a social problem. It is popular because toluene induces pleasant sensations, relaxation, and tranquility. Exposure to high concentrations resulting in severe toluene intoxication, except during sniffing, is observed infrequently and clinical and toxicological observations in cases of serious intoxications are scarce.

We describe two patients with severe, acute toluene intoxication. Special attention is paid to the metabolism of toluene in man and to the choice of reference parameters to monitor intoxication.

Case histories
Two men (aged 43 and 34) had tiled a small swimming pool (6·0 m long, 0·90 m broad, and 2·5 m deep) to be used for exercise programmes in a rehabilitation clinic. Subsequently they had made the joints of cement between the tiles resistant to bleaching solutions with a special glue. The next day they removed the excess of glue from the tiles with toluene. Patient A started work at 0900 and patient B at 1000. By coincidence, at 1215 both patients were found by their colleagues lying at the bottom of the pool.

The symptoms observed when they were found were stufpaction, paresis, and amnesia. They were lifted from the bottom of the pool and subsequently admitted to the University Hospital, Utrecht.

Both patients had previously been in good health. Physical examination was carried out one hour after they were found.

PATIENT A
Patient A had mucosal irritation of the eyes and slurred speech. He was stuporous and unable to walk or sit. Blood pressure was 140/70 mm Hg and pulse 56 BPM. Auscultation of heart and lungs showed no abnormalities; on examination the abdomen was normal.

There were no haematological disorders. The concentration of serum creatinine was 78 µmol/l, urea 7·1 mmol/l, sodium 141 mmol/l, potassium 4·5 mmol/l, chloride 105 mmol/l, and bicarbonate 24 mmol/l. Total bilirubin concentration, alkaline phosphatase activity, serum aspartate aminotransferase activity, and serum alanine aminotransferase activity were within the normal range. Blood gases, while room air was breathed, were PaO₂ 71 mm Hg and PaCO₂ 41·9 mm Hg. Arterial pH was 7·39. The anion gap was 16·5 mmol/l (normal < 13 mmol/l). Blood toluene concentration was 4·1 mg/l; the table shows the urinary ortho-, meta-, and para-cresol and phenol concentrations after exposure. The electrocardiogram showed a sinus bradycardia. The chest x ray film was normal.

The amnesia lasted from about 1015 until 1330. About four hours after being found, patient A experienced increasing pain in his right arm. Physical examination showed no fractures, contusions, or haematomas and the pain was probably caused by distortion of the elbow when he was lifted out from

| Urinary excretion of some metabolites of toluene (mg/g creatinine) |
|------------------------|-----|-----|-----|-----|
| o-Cresol               | m-Cresol | p-Cresol | phenol |
| Patient A              |     |     |     |     |
| 9–6 h                  | 10·7| 2·62| 52  | 3·57|
| 6–18 h                 | 6·2 | 2·43| 57  | 4·53|
| 18–24 h                | 12·4| 1·77| 38  | 3·68|
| Patient B              |     |     |     |     |
| 0–6 h                  | 6·9 | 2·29| 50  | 2·20|
| 6–18 h                 | 3·0 | 1·34| 35  | 2·04|
| 18–24 h                | 10·5| 2·57| 56  | 3·57|

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the pool. Presumably, the pain was not felt until after several hours because of the analgesic effect of the toluene. He was discharged from the hospital five hours after being found and his only complaint then was pain in his right elbow.

**PATIENT B**

Patient B had mucosal irritation of the eyes, was drowsy, and was just able to walk. He had normal speech and complained of headache. Blood pressure was 120/80 mm Hg, pulse rate 116 BPM. Auscultation of the heart showed a systolic murmur in the left parasternal, third intercostal space (grade I/VI). Auscultation of the lungs showed no abnormalities. On examination of the abdomen the liver was just palpable.

The haemoglobin concentration, platelets, and white cell counts were within the normal range. The concentration of serum creatinine was 76 μmol/l, urea 4.4 mmol/l, potassium 4.5 mmol/l, sodium 140 mmol/l, chloride 106 mmol/l, and bicarbonate 24.2 mmol/l. Total bilirubin concentration, alkaline phosphatase activity, serum aspartate aminotransferase activity, and serum alanine aminotransferase activity were within normal ranges. Blood gases, while room air was breathed, were: PaO₂ 85 mm Hg, PaCO₂ 39 mm Hg. The arterial pH was 7.40. The anion gap was 14.3 mmol/l. The blood toluene concentration was 2.2 mg/l. The table shows the urinary o-₃, m-, and p-cresol, and phenol concentrations. The electrocardiogram showed a sinus tachycardia. The chest x ray film was normal.

The duration of amnesia in this patient was from about 1015 to 1245. He recovered within two hours and was discharged from the hospital in good health five hours after being found.

Both patients were investigated 24 hours and one week after the exposure. During this period no haematological disorders or renal and hepatic involvement were observed. In the first week after exposure the first patient sometimes had periods of slight pain in his right elbow but thereafter, he was free of complaints.

**Materials and methods**

The toluene concentration in blood was determined by capillary gas chromatography with flame ionisation detection. After the blood sample had been collected, the blood was put into a special head space vial of glass with a content of about 45 ml, closed with a rubber membrane with a Teflon lining, and stored at 4°C. The vial may be stored for several days without loss of toluene. A gas tight syringe of 1000 μl (Precision Sampling type Pressure Lok) was used for injection of head space air. From the head space air, an aliquot of 200 μl was used for gas chromatographic analysis on a Carb Erba 4130 GC (Carb Erba Instruments, Milan, Italy). Separation took place on a 26 m glass capillary column WCOT CP Sil 5 CB (Chrompack, Middelburg, NL) with an internal diameter of 0.34 mm and a film thickness of 1.3 μm. Hydrogen was used as carrier gas and was set at a pressure of 1.8 bar. Column temperature was programmed from 40°C to 160°C at a rate of 20°C/min. For quantifying the results, an external calibration curve was made by using head space analysis of calibration samples of 0.2 and 10 μl of toluene dissolved in 1000 ml H₂O. This mixture was vigorously shaken for 15 minutes. Next, the samples and the calibration samples were incubated at room temperature for two hours. A sample without toluene showed no detectable toluene concentration. The detection limit was < 10–50 μg/l. Subsequently, the toluene concentration of the samples were determined and converted by using the calibration curve.

O-₃, m-, and p-cresol and phenol were determined in urine by gas chromatography with flame ionisation detection. The cresols and phenol were extracted from urine with liquid-liquid extraction after acidic hydrolysis. To 5 ml of urine, 1 ml of internal standard solution (800 mg 3,4-dimethylphenol per litre of water) and 1 ml of concentrated hydrochloric acid were added. The urine sample was hydrolysed by heating the mixture in a water bath of 70°C for two hours. After cooling down to room temperature, 1 ml of isopropyl ether was added. The mixture was vigorously shaken for 15 minutes and subsequently centrifuged. The supernatant isopropyl ether was transferred into a sample vial and 2 μl was used for a gas chromatographic analysis. Separation was on a borosilicate glass column (6 ft long, 2 mm internal diameter) packed with 80/100 mesh Carbopack C coated with 0.1% SP-1000 (Supelco). Helium (30 ml/min) was used as a carrier gas. Typical retention times were of phenol 1.52 minutes, of o- 3.92, of m- 4.54, and of p-cresol 4.88, and of 3,4 dimethylphenol 17.43.

**Discussion**

The history in these cases was suggestive of exposure to toluene. The symptoms of stupor, paresis, and amnesia were compatible with severe toluene intoxication and caused by severe depression of the central nervous system.

Solid evidence for toluene intoxication was provided by the blood toluene concentration. The blood toluene concentration two hours after exposure was in patient A 4.1 mg/l and in patient B 2.2 mg/l. The blood toluene concentration is below the detection limits in unexposed individuals. Carlsson found, 90 minutes after the end of the exposure to toluene, a blood toluene concentration of 18–30%, of the concentration at the end of the exposure. After a period of 90 minutes, Veulemans found a toluene concentration around 30%, of the concentration at the end of
the exposure; after 120 minutes, the concentration
was 25% lower. The decrease of toluene concentration is
most pronounced within the first few minutes,
further decline occurs more gradually. From these
data it may be concluded that the blood toluene
concentration in both patients was much higher at
the end of the exposure than that determined sub-
sequently. Toluene blood concentrations in post-
mortem specimens of fatal cases have varied from 10
to 33 mg/l.1,4

Hepatic and renal involvement was not noticed.
The anion gap was slightly increased (in patient A
16.5 mmol/l and in patient B 14.3 mmol/l) either
from distal tubular acidosis or increased concentra-
tion of the metabolites of toluene. Fischman and
Oster and Patel and Benjamin described distal
tubular acidosis in patients who were exposed
cronically to high concentrations of toluene.57
Fischman and Oster suggested that an increased
anion gap could also be caused by an increased
concentration of the metabolites of toluene such as
benzoic acid or hippuric acid. Since the present
patients were not chronically exposed to high toluene
concentrations the anion gap seems to have been
caused by an increase in the concentration of
metabolites of toluene.

The high toluene concentration in the swimming
pool provided evidence that both patients were
seriously exposed to toluene. Three hours after the
patients were rescued the toluene concentration was
> 7000 mg/m³ (= 1842 ppm) at the edge of the pool.
A more precise calculation could not be made by the
fire brigade because the concentration was deter-
mined by Dräger tubes. Since toluene is heavier than
air it had probably sunk to the bottom of the pool
where the concentration was presumably even higher.

The acute effects observed in man of a single, short
term exposure to a toluene concentration of 1500 mg/
m³ are headache, dizziness, irritation of the throat
and eyes, lachrimation, skin paraesthesia, incoordina-
tion, and mental confusion. With exposure to 3000
mg/m³ the symptoms can be nausea, confusion,
ataxia, amnesia, serious reduction in reaction time,
and lack of self control. The effects after exposure to
15 000 mg/m³ cause rapid impairment in reaction
time and coordination. Exposure of one hour or more
to this concentration may lead to narcosis and
probably to death.6

Toluene is readily absorbed by inhalation and
ingestion and rapidly metabolised by two oxidative
routes. The major route is oxidation of the aliphatic
chain. Approximately 80% of an absorbed dose is
metabolised by this route with the formation of
benzoic acid which is further conjugated either with
glycine to hippuric acid, or with glucuronic acid to
benzoic acid and hippuric acid. The minor route is oxida-
tion of the aromatic ring which potentially results in
formation of o-, m-, and p-cresol. The cresols are
excreted in urine as their corresponding glucuronide
and sulphate conjugates.8

Since several food products contain benzoic acid,
urinary hippuric acid excretion is related to intake of
benzoic acid via the food. This causes a considerable,
intraindividual variation. In a group of 39 unexposed
individuals urinary hippuric acid excretion ranged
between 0·086 and 2·340 g/g creatinine (mean 0·739
g/g creatinine).10 On a group urinary hippuric acid
excretion may be used to monitor exposure to toluene
but on an individual basis it is an unambiguous index
only after exposure to toluene concentrations above
3040 mg/m³ (= 800 ppm).11 For similar reasons the
excretion of benzoic acid is not a suitable index of
toluene exposure.

Para-cresol is a normal constituent of urine of
individuals not exposed to toluene. In 85 male human
volunteers we determined the urinary para-cresol
excretion and the results are shown in fig 1. On the
basis of these results, we calculated the reference
to be 3·3–63 mg/g creatinine. Obviously p-
cresol is not a suitable index of exposure to toluene
either. For the same reason, urinary phenol excre-
tion, which was determined in the same group of
male healthy volunteers, is not an adequate indicator
of exposure to benzene (fig 2); reference values for
urinary phenol excretion were to be 0·8–16 mg/g
creatinine.

In most published analytical procedures for deter-
mining cresols in urine, m- and p-cresol are not
separated. Our analytical procedure, however, was
able to separate all three cresols. Therefore the
excretion of o- and m-cresol, which are not normal
constituents of the urine,12 could be monitored as
well. In the rat metabolites of toluene included o- and
p-cresol but not m-cresol.13 In man it has been
assumed that only o- and p-cresol are formed after
exposure to toluene.14 15 A linear relation between
exposure to toluene and urinary o-cresol excretion

Figure 1 Frequency distribution of urinary p-cresol
excretion in 85 male volunteers. Figures on concentration axis
indicate upper limits of respective classes. Reference values
were determined by a non-parametric method.
was observed up to a toluene concentration in air of 120 ppm.16 Therefore, o-cresol is a potentially useful means by which to monitor toluene exposure.

In both patients the urinary excretion of all three cresols was determined as were urinary phenol excretion (table). Since benzene exposure was not involved, the urinary phenol excretion may intra-individually indicate normal renal excretion. Both the urinary excretion of phenol and of p-cresol were within the respective calculated reference values. P-cresol excretion, therefore, cannot be used to monitor toluene exposure. As expected from the high toluene exposure, o-cresol was excreted in the urine. M-cresol was also found in concentrations 0.15–0.45 times those of o-cresol. To our knowledge this has been observed only once before.17 Evidence exists that formation of m-cresol from toluene is highly unlikely14,15 but with high toluene exposure, as in the present cases, other metabolic pathways may be activated. From these results it seems that urinary o-cresol excretion is a selective means by which to monitor toluene exposure even at low levels. In addition, high level toluene exposure may be assessed on the basis of the urinary m-cresol excretion. The presence of m-cresol in the urine of both patients was confirmed by gas chromatography-mass spectrometry. The cresols were separated on a capillary column (length 25 m, internal diameter 0.23 mm) coated with CP Wax 57 CB (Chrompack) using a quadrupole gas chromatograph-mass spectrometer (Finnigan 4000) operated in electron impact mode. The presence of m-cresol as well as o- and p-cresol was confirmed in all urine samples.

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Figure 2 Frequency distribution of urinary phenol excretion in 85 male volunteers. Figures on concentration axis indicate upper limits of respective classes. Reference values were determined by a non-parametric method.
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