koorts, anemie en lymfadenopathie. Het is beschreven dat deze zeer zeldzame aandoening voorkomt bij een gesystematiseerd B-cel non-Hodgkin lymfoom (2).
Het gesignaleerde probleem met de detectie van het paraproteïne in de immunofixatie werd nader onderzocht door de samenstelling van het fixatief voor het eiwitspectrum in de IFE (10% azijnzuur, 5% sulfosalicylaat) te wijzigen. Verhoging van de concentraties van beide componenten tot maximaal respectievelijk 20% en 10% had vrijwel geen effect (data niet getoond). Toepassing van het voor eiwitspectra gebruikelijke fixatiemiddel (20% azijnzuur, 30% methanol) gaf een goede fixatie van de zware keten op de IFE agarosegel. Fixatie met methanol is kennelijk essentiëel voor de detectie van dit eiwit. Een snel diffunderend fixatiemiddel is echter niet toepasbaar in de standaard fixatieprocedure, waarbij de incubaties van de verschillende lanen met het fixatief en de verschillende anti-immuunglobulineantistoffen tegelijkertijd plaatsvindt. Dit zou namelijk leiden tot ongewenste fixatie van eiwitten in de naastliggende laan.

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An unexpected intoxication with an analgesic from abroad

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Case history

A 37-year old female (62 kg) was found in a state of coma with seizures. On arrival in the hospital (approx. 22.00 p.m.) she was intubated and reanimated because of respiratory arrest. Seizures were treated with diazepam i.v. Blood and liquor samples were drawn and a CT-scan was made. Arterial blood pH was 7.19, pCO_2 6.1 kPa and bicarbonate was 17 mmol/l indicating combined respiratory and metabolic acidosis. Additional findings were 0.4 g/l ethanol, and 270 mg/l paracetamol for which she was treated with N-acetyl-l-cysteine i.v. Liquor analysis and the CT-scan gave no clues to the cause of coma and convulsions. Later that night information was obtained that she was suffering from severe headaches accompanied by dizziness, and that she was receiving fluvoxamine as an antidepressant and incidentally zopiclone as a hypnotic. At that time, a polydrug overdose was suspected and gastric lavage was started (01.30 a.m.). No tablet residue was found in the aspirate. Treatment was continued and consisted of monitoring vital functions. In the blood sample taken at 01.30 a.m., the pH was 7.24 and 2.4 mmol/l lactate was found, again indicating metabolic acidosis. At 02.45 a.m. the patient became responsive and regained consciousness in the following hours. At 06.00 a.m. she was able to recall the day before and told the physician that she had taken two beers at about 18.00 p.m. the evening before and a few Distalgesic tablets. She also told to have obtained the tablets from a relative abroad. The next day a toxicological analysis was requested of the blood sample taken on admission, i.e. about 4 hours post-ingestion. The results confirmed the presence of dextropropoxyphene (0.8 mg/l), norpropoxyphene (1.2 mg/l), and fluvoxamine (0.43 mg/l). Zopiclone was not found. The patient made a full recovery.

Discussion

Distalgesic is not available in the Netherlands. Active ingredients are paracetamol (325 mg/tablet) and dextropropoxyphene (32.5 mg/tablet). Dextropropoxyphene has a low therapeutic index and ingestion of 10-20 times the usual dose can produce an intoxication with fatal outcome (1-4). Blood concentrations of over 2 mg/l of dextropropoxyphene relate to fatalities and lower lethal values have been reported when dextropropoxyphene was used in combination with ethanol or benzodiazepines. Dextropropoxyphene intoxications resemble those of morphine except that seizures are prominent. Vital functions should be monitored and seizures can be treated by diazepam i.v. In severe cases, naloxone is indicated to resolve respiratory depression. Hemodialysis and hemoperfusion are not indicated because of dextropropoxyphene's large volume of distribution (1-3).
Paracetamol and dextropropoxyphene are quickly absorbed and peak values in blood are usually obtained within 1-2 hours after ingestion (1-3). In cases of ingestion of a large number of tablets, their

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absorption may be significantly retarded and continue for many hours. The reason for this is the ability of dextropropoxyphene to reduce gastro-intestinal activity. This effect of dextropropoxyphene has recently been suggested as the cause of a delayed toxic paracetamol concentration in the blood (5). Dextropropoxyphene undergoes extensive first-pass metabolism to norpropoxyphene and this explains the amount of this metabolite found in the 22.00 p.m. blood sample. Volumes of distribution are approx. 0.95 l/kg for paracetamol and approx. 14 l/kg (10-18 l/kg) for (nor)propoxyphene (1). Based on the 22.00 p.m. values (i.e. 4 hours post intake), the approximate doses of paracetamol and dextropropoxyphene ingested can be estimated to be 16 g and 1.7 g, respectively. The ratio of these amounts corresponds well with the ratio of the two drugs in Distalgesic tablets. This suggests that the patient had not taken additional paracetamol. The doses calculated correspond to a number of approximately 50 Distalgesic tablets ingested.

Fluvoxamine is supposed to be relatively safe. No adverse effects may be expected from a blood level of 0.43 mg/l (therapeutic range up to about 0.2 mg/l). Fluvoxamine, however, appears to inhibit cytochrome P-450 isoenzymes 1A2 and to a lesser extent 2D6 (6-13). The demethylation of dextropropoxyphene by cytochrome P450 might, therefore, have been inhibited in our patient. Accumulation of dextropropoxyphene is not apparent in the blood sample taken on admission as the ratio of dextropropoxyphene to its metabolite is similar to values reported by others in case histories (1-4). We conclude that fluvoxamine did not inhibit the demethylation of dextropropoxyphene in the patient during the acute phase of the intoxication. The concentrations of dextropropoxyphene and metabolite found explain coma, respiratory depression, and seizures. The use of Distalgesic is dissuaded because of its low therapeutic index and high mortality in overdose cases (14).

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Summary

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An almost fatal intoxication is described with Distalgesic, which contains paracetamol and dextropropoxyphene. The patient presented with coma, respiratory depression and seizures. The paracetamol concentration in the blood sample taken on admission, 4 hours after presumptive oral intake, was 270 mg/l and treatment with N-acetyl-l-cysteine (i.v.) was started. Dextropropoxyphene and norpropoxyphene concentrations were 0.8 mg/l and 1.2 mg/l, respectively, on admission. Fluvoxamine was also found in a concentration of 0.43 mg/l. The patient was treated conservatively with monitoring of vital functions. The patient became responsive 9 hours after ingestion of the tablets. Further recovery was without complications.

Keywords: intoxication; human; dextropropoxyphene.