CASE REPORT

Intoxication with a tropenol ester

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Background
While the effects of medicinal products are investigated in depth before approval, often very little is known about the intermediates occurring during synthesis. The pharmacological properties of these intermediates can differ substantially from those of the end product.

Aims
To describe a work accident involving intoxication with such an intermediate, tropenol ester.

Case report
A healthy 40-year-old chemical-technical operative erroneously used a scrubbing brush that had just been used to clear up tropenol ester, contaminating his work clothes. Presumably, contact was made with his skin when removing his work clothes later. Shortly thereafter, he developed signs of anticholinergic intoxication with mydriasis, dry mouth, abnormal coordination and later sleepiness and seizures. The patient received intensive medical treatment. Two weeks later, the anticholinergic symptoms had subsided. Qualitative analysis of a urine sample showed traces of tropenol ester. The substance is a muscarinic acetylcholine receptor antagonist.

Conclusions
The clinical symptoms and biomonitoring suggest that intoxication with tropenol ester had occurred, which, as a tertiary amine, readily passes through the blood–brain barrier. The protracted course suggests high affinity for the receptor. Appropriate safety precautions must be taken when handling research substances and intermediates of unknown toxicity.

Key words
Anticholinergic; antimuscarinic; intoxication; occupational; tropenol ester.

Introduction
Adverse effects of medications, but not their precursors, are investigated before marketing authorization. However, these precursors can be relevant to exposed workers. Toxicity can differ considerably from that of the end products. We report on an intoxication incident with the muscarinic acetylcholine receptor-antagonist tropenol ester (di-(2-thienyl)glycolic acid tropenol ester), a precursor of tiotropium bromide [1], which is used as a bronchodilator.

Case report
A healthy 40-year-old chemical-technical operative was working in the production of brotizolam, which is used as a hypnotic. Exposure to traces cannot be excluded. He spent some time in the adjoining production area where tropenol ester was manufactured within a closed system. At the end of his late shift, he showered and dressed in his street clothes. On the way home, he showed signs of abnormal coordination and drowsiness. At home, he had a seizure. His wife’s description suggests a grand mal convulsion. The emergency physician noted that he was extremely drowsy, breathing spontaneously, and his pupils were fixed and dilated. Subsequently, he showed signs of hypoxia. After two failed attempts by the emergency physician to intubate, the intensive care unit eventually succeeded in doing so. The next day, the patient was given artificial ventilation. A chest radiograph showed pulmonary oedema. Mucous membranes were dry. Urine drug screening found qualitative evidence of tropenol ester. One week later, neurological examination found no remarkable findings except for mydriasis. A computed tomogram of the skull was normal. Ten days after intoxication, his pupils were still fixed and dilated, and the mucosa dry. Liver enzymes were mildly raised. The patient later reported dilated pupils, photophobia, problems with reading and a dry mouth, for 2 weeks, after the accident. One week later, the pupils had returned to normal and reacted normally to light. Three months

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later, the patient reported impaired concentration for a few weeks after the intoxication. He felt ‘contractions’ now and again in the region of the left temple, but only at rest. The patient had worked for 2 months as a chemical technician in another production plant without problems. Neurological and psychiatric examinations including electroencephalogram (EEG), acoustic evoked brainstem potentials, velocity of nerve conduction of popliteal and sural nerves, the extra- and transcranial Doppler sonography of arteries supplying the brain and Mini-Mental Status test [2] were normal. Ten months after the accident the patient reported no complaints.

During occupational examination, the patient reported that a drop of tropenol ester dissolved in methylene chloride had fallen on his arm while dismantling a tube 1 year previously. Shortly thereafter, he had noticed that his mouth was dry and vision blurred. His pupils were dilated and his fine motor activity impaired. Symptoms of intoxication had subsided after 3 days.

The plant conducted lengthy investigations to establish the exposure pathway. It transpired that the patient had used a scrubbing brush contaminated with tropenol ester that had not been properly disposed of. His working clothes were probably contaminated with the tropenol ester. We assume that contact with his skin occurred while removing his work clothes at the end of his shift.

Discussion

Anticholinergic toxicity may present as atropinic symptoms including dry mouth, thirst, fixed and dilated pupils, flushed face, fever, skin becoming hot, dry and red, and tachycardia. Speech and swallowing may be impaired in association with blurred vision. Severe overdoses may lead to a hallucination-like delirium, tremors, convulsions, coma, respiratory failure or cardiovascular collapse [3]. We have limited knowledge of the toxicological properties of tropenol ester, including its possible metabolites. Tropenol ester is similar to butylscopolamine, which is used therapeutically as an antispasmodic. However, tropenol ester, unlike butylscopolamine, is a tertiary amino and not a quaternary ammonium compound. So tropenol ester readily penetrates the blood–brain barrier. This is corroborated by our patient’s observation that he developed central nervous anticholinergic symptoms when a drop of liquid containing tropenol ester fell on his arm.

In another report, a chemical laboratory technician was exposed to tropenol ester dust. He developed bilateral mydriasis persisting for 3 weeks [4]. The prolonged course in both cases suggests that tropenol ester has a high receptor affinity. This is confirmed by experimental findings with rabbits. A dose of 1 mg/kg body weight caused EEG synchronization still detectable after 20 h (unpublished experiments by the manufacturer). So far, cloning studies have identified five different genes putatively encoding the muscarinic receptor subtypes M₁–M₅ [5,6]. Pharmacological evidence suggests four muscarinic acetylcholine receptor subtypes M₁–M₅ [5]. In vitro experiments with tropenol ester revealed inhibitory constants (K) for M₁, M₂ and M₃ receptors of 0.1, 0.41 and 0.45 nmol/l, respectively (unpublished experiments by the manufacturer). These constants also support high receptor affinity of tropenol ester.

Most tissues and cell types express at least two or more muscarinic receptor subtypes [7]. The M₁ receptor predominates in ciliary processes and the iris sphincter of the human eye [8]. We therefore conclude that the long-lasting mydriasis was probably due to an inhibition mainly of muscarinic M₁ receptor activity. Our assumption is corroborated by the inhibitory constant of 0.45 nmol/l measured in vitro.

From our investigations, it seems very likely that the patient suffered from tropenol ester intoxication. Exposure was confirmed by urine analysis. Clinical symptoms suggested intoxication with an anticholinergic compound. No alternative cause was apparent. The reason for the minor liver function test increase is unclear.

Appropriate safety precautions must be taken when handling research substances and intermediates of unknown toxicity. This was the case in the plant in which the tropenol ester was produced within a closed system. Handling was regulated by in-house specifications and organizational measures, including keeping the entire plant clean. Employees were given detailed instructions. The work accident described is an example of human error. ‘Human’ factors may preclude the elimination of such accidents.

Key points

- Diagnosis of intoxication may be difficult if the toxicity of the compound is not sufficiently investigated.
- It can be difficult to determine exposure pathways, especially if the substance is biologically highly potent.
- Appropriate safety precautions must be taken when handling research substances and intermediates of unknown toxicity. Preventive measures should account for the possibility of human error.

Conflicts of interest

M.S. is the company doctor of the plant where the accident happened. A.M. and S.L. have no conflict to declare.
References


Why I am doing the GCC again

‘What do you understand by the term “walk the talk”?’ was one of the more unconventional questions at my interview for the position of Communication Consultant for the SOM. Having garbled my response and been successfully appointed, I am now literally walking the talk on behalf of the society.

I am just about to embark on my third year as a participant in the Global Corporate Challenge (GCC). It’s a workplace health initiative, and this year, as part of the society’s team of seven, I’ll be joining 180,000 other participants. The aim is to walk 10,000 steps a day. The programme requires you to wear a pedometer for 16 weeks and input your steps into the GCC website. You then go on a virtual team journey around the world and track your team’s performance against others and monitor your own achievements.

For the first time, this year I’m really looking forward to it. In Year 1, I was shocked that my usual day involved walking about 4000 steps, so I needed to make some changes to my busy schedule. This was easier for me when I went into the office—I just walked from the mainline train station instead of getting on the tube. When working from home, I had to make an effort to go out at lunchtime. The amazing thing was how walking every day made me ‘generally happier’. It also compelled me to think about what I ate. The realization of how much it takes to ‘walk-off’ a two-finger Kit-Kat made me ask whether I really wanted to eat one. Still, I was delighted to lose 8 kg during the 16-week period.

The initiative is great because it inspires the whole workplace team. I really enjoyed the encouragement I received from my colleagues. Undertaking a personal activity together adds to the team spirit in the office. ‘How many steps so far?’ I would enquire of Dr John East, the society’s medical director, as he entered the office slightly breathless from climbing the stairs. MSN banter reminded us to enter our steps. I felt that if I had a few days when I didn’t do my allocated steps I would be letting the whole team down—inspiration for me to make them up at the weekend.

For me, the success of the initiative has been in Year 2. After the first year, I found that I quickly reverted to my old ways. You don’t need to be Sherlock Holmes to guess that I lost the fitness and other benefits and regained the weight. The second year I incorporated other activities as well as walking and started going to the gym. This time I have sustained it. I’d recommend any company to get their staff involved. The GCC website (www.gettheworldmoving.com) gives information on the benefits for the individual and for the employer. A big personal thank you to Dr David Batman, formerly from Nestlé, who has supported the society each year and enabled us to enter a team.

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