

Case report from the GTFCh working group "Clinical Toxicology"

Acute Poisoning with Dapsone – A Case Report

Thomas Kraemer^a, Liane D. Paul^a, Christiane Jochum^b and Hans H. Maurer^a

^a *Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, University of Saarland, D-66421 Homburg (Saar), Germany*

^b *Internal Medicine, Bundesknappschaftsklinik, D-66346 Puettlingen, Germany*

Summary

Acute poisoning from excessive dapsone (4,4-diaminodiphenylsulfone) intake is uncommon in Europe. However, with the increasing use of dapsone for diseases other than leprosy and dermatitis herpetiformis, such as acne vulgaris, psoriasis, and pneumocystis carinii pneumonia infection in acquired immunodeficiency syndrome, clinicians should be aware of its toxic potential. This report describes a case of dapsone poisoning for suicidal purpose resulting in severe cyanosis with an elevation in methemoglobin concentration. Other symptoms were nausea and vomiting. Patient improved with intravenous methylene blue. Methemoglobin level after application of methyleneblue antidote was 26%. Hemoglobin values slightly decreased from 12.5 g/dL to 10.2 g/dL over five days with total bilirubin levels increasing from 1.25 mg/dL to 4 mg/dL. Additional treatment consisted of multiple-dose activated charcoal treatment over five days and parenteral diphenhydramine against vomiting. The patient recovered ad integrum and was transferred to a psychiatric hospital.

Introduction

Acute poisoning from excessive dapsone (4,4-diaminodiphenylsulfone) intake is uncommon in Europe. However, with the increasing use of dapsone for diseases other than leprosy and dermatitis herpetiformis, such as acne vulgaris, psoriasis, and pneumocystis carinii pneumonia infection in acquired immunodeficiency syndrome, clinicians should be aware of its toxic potential. In the last five years, several case reports were published dealing with this topic (1-9). This report describes a case of dapsone poisoning for suicidal purpose resulting in severe cyanosis with elevation in methemoglobin concentration.

Case details

A 24 years old woman was admitted to the ICU. She showed symptoms of severe cyanosis, nausea and vomiting. The emergency doctor reported, that she admitted ingestion of various medicaments with suicidal intention being in a domestic conflict situation. Blood and urine samples of the patient were sent to our toxicological laboratory.

The patient was treated with single dose administration of methyleneblue (2 mg/kg body mass), which led to marked improvement of the cyanosis. Nausea and vomiting could be stopped by administration of parenteral diphenhydramine. Multiple-dose activated charcoal treatment was conducted over five days. The patient completely recovered from the dapsone poisoning and was transferred to a psychiatric hospital.

Analytical methods

The samples were analyzed according to our standard systematic toxicological analysis procedure (STA) (10-12). Screening in urine was performed using GC-MS after acid hydrolysis, liquid-liquid extraction and acetylation. The plasma sample was extracted at native pH and at alkaline pH after addition of sodium hydroxide (internal standard trimipramine-d3). The combined extracts were analyzed also by GC-MS. Quantification of dapstone in plasma was performed by LC-MS using this routine plasma extract. For details on our standard LC-MS quantification procedure see references (13-15).

Results

Dapstone could easily be detected in plasma and urine by GC-MS using the routine STA procedure. Figure 1 shows the corresponding mass spectra of dapstone and its bis-acetyl derivative. The bis-acetylated dapstone is not only a derivatization product but also a metabolite of dapstone. The mass spectra will be integrated in the next update of our handbook and library (16,17). Besides dapstone, ibuprofen could be detected in plasma and urine.

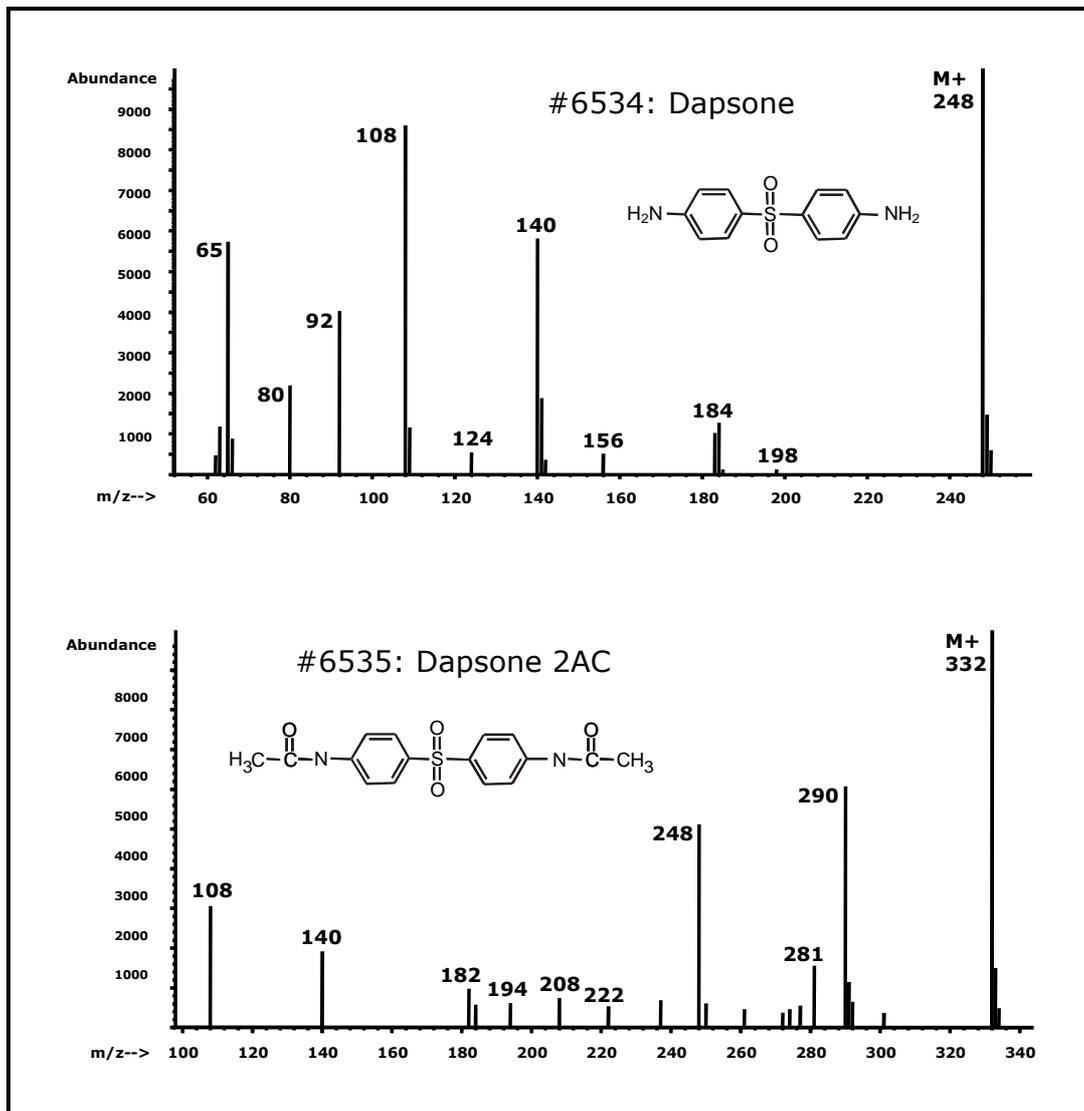


Figure 1: EI mass spectra of dapstone and its bis-acetylated derivative.

Quantification was achieved by LC-MS. The concentration measured was 18 mg/L, which is in a high toxic range (therapeutic range 0.5-2 mg/L). Figure 2 shows LC-MS mass chromatograms for dapsone (ions m/z 249 and 156) and the internal standard trimipramine-d3 (m/z 61 and 298). Clinical symptoms corresponded well with the analytical finding of a dapsone poisoning.

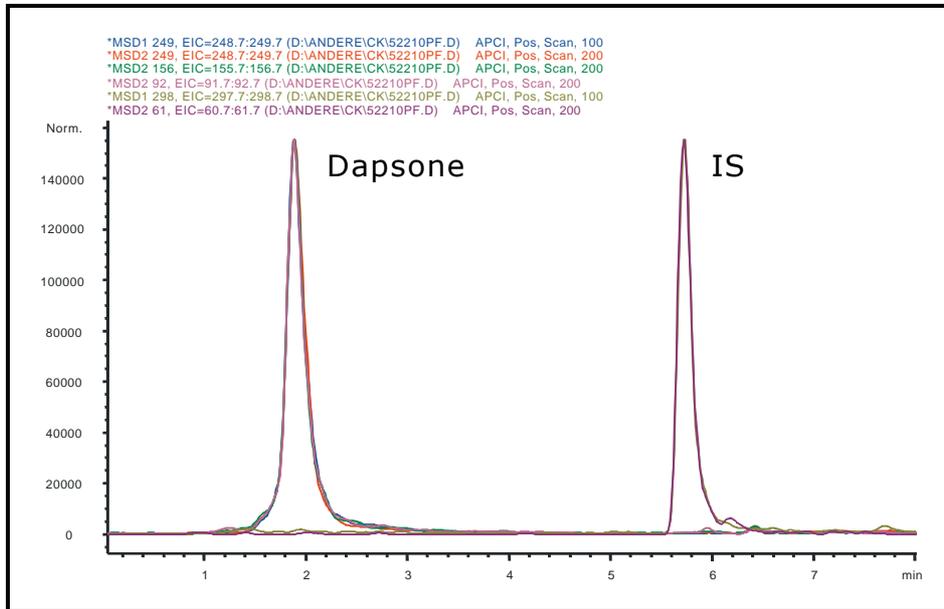


Figure 2: Merged and normalized mass chromatograms with the ions m/z 249 and 156 (dapsone) and m/z 61 and 298 (internal standard) indicating 18 mg/L of dapsone.

Table 1: Clinical symptoms in correlation with methemoglobin concentrations in blood (according to ref. (18))

Conc. of methemoglobin	Clinical Symptoms
<15%	Mostly no symptoms
15-20%	Cyanosis, headache, drowsiness
20-45%	Marked cyanosis, nausea
45-70%	Severe cyanosis, vomiting, convulsions
>70%	Death

Table 1 lists clinical symptoms in correlation of the methemoglobin concentration in blood. Unfortunately, initial methemoglobin blood concentration was not determined. The severe cyanosis, that could be observed at admission to the hospital, improved rapidly after i.v. administration of methyleneblue. After administration of the antidote methemoglobin concentration was 26 %.

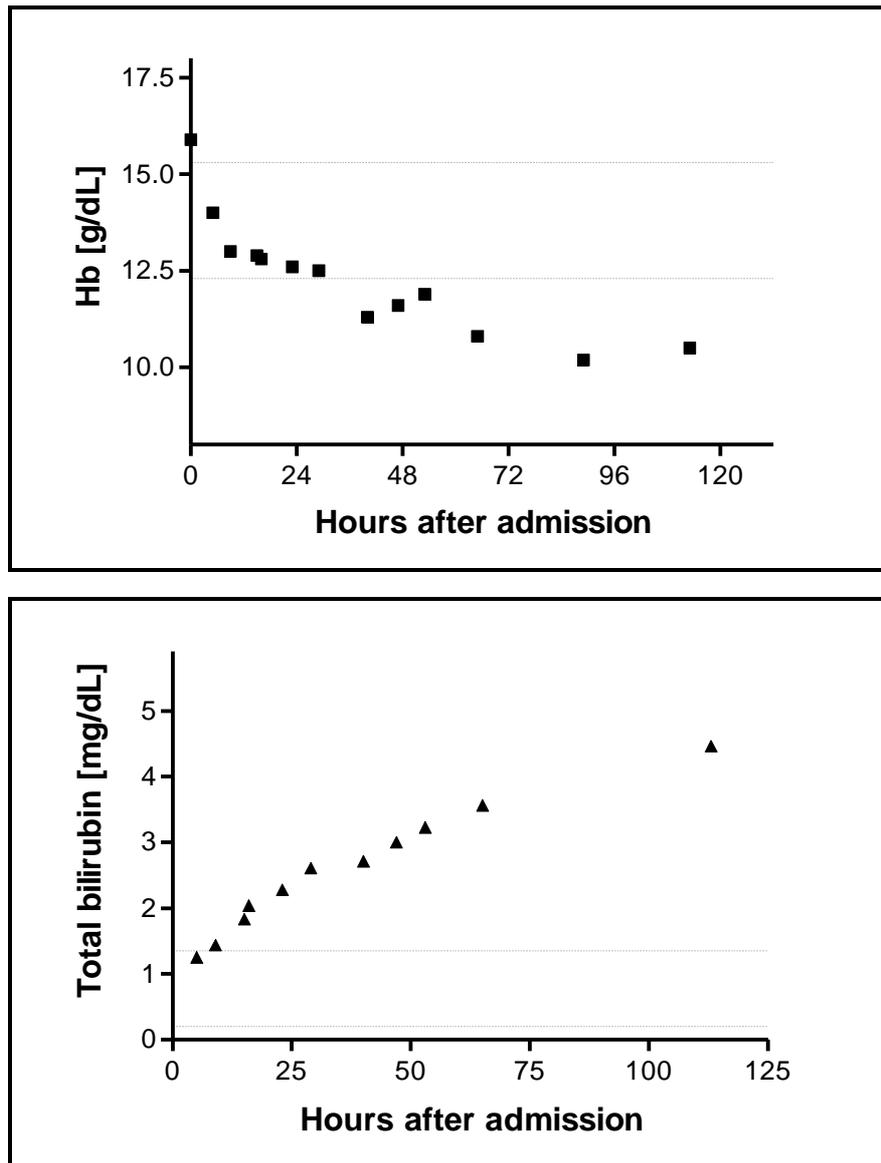


Figure 3: Time course of hemoglobin level (upper part) and of total bilirubin concentration (lower part) in patients blood (dotted lines indicate normal range).

Nausea and vomiting could be sufficiently treated with diphenhydramine. Multiple-dose activated charcoal treatment was maintained for five days. As methemoglobin levels decreased to normal levels during this time and as cyanosis did not reappear, a further methyleneblue dosis was not necessary. As shown in Figure 3, hemoglobin concentration in blood decreased from an initial value of 15.9 g/dL to 10.5 g/dL after 113 hours. In the same time range total bilirubin values increased from 1.3 mg/dL to 4.5 mg/dL. The patient completely recovered and was transferred to a psychiatric hospital five days after admission.

Discussion

Analytical detection of dapsone could easily be achieved by routine STA procedures using GC-MS. For quantification purposes LC-MS was more suitable due to the high polarity of dapsone. Dapsone poisonings are uncommon in Europe. If they occur, massive clinical symptoms like severe cyanosis, nausea and vomiting are to be expected. Severe poisonings with methemoglobinemia over 70 % usually are fatal. Early administration of the antidote

methyleneblue usually leads to rapid improvement of the cyanosis. Because of the long half-life of the toxicant, repeated administration of methyleneblue may be necessary (19). In our case, single dose administration of the antidote was sufficient.

The decrease of hemoglobin levels in blood may also be explained by dapsone. It is well known that dapsone is responsible for hemolysis processes (18). In this case, excessive dapsone levels may have lead to the corresponding decrease in hemoglobin levels. The hemoglobin that is released by hemolysis is metabolized in the liver. Correspondingly, bilirubin levels increase, as observed in the patient.

Poisoning with dapsone is one of the few indications for multiple-dose activated charcoal treatment according to the "Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning" of the American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists (20). They stated that based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all of these drugs there are data to confirm enhanced elimination, though no controlled studies have demonstrated clinical benefit. In our case, multi-dose activated charcoal treatment was conducted over five days, thus enterohepatic circulation of dapsone could effectively be interrupted (21,22). Persistent vomiting was treated with parenteral diphenhydramine. Since ingestion of dapsone was for suicidal purpose, patient was transferred to a psychiatric hospital for corresponding therapy.

References

1. Falkenhahn M, Kannan S, O'Kane M. Unexplained acute severe methaemoglobinaemia in a young adult. *Br J Anaesth* 2001;86:278-280.
2. Lewis S, Clark P. Diagnostic confusion caused by dapsone-induced methaemoglobinaemia. *Br J Anaesth* 2001;87:802-803.
3. Carrazza MZ, Carrazza FR, Oga S. Clinical and laboratory parameters in dapsone acute intoxication. *Rev Saude Publica* 2000;34:396-401.
4. Solheim L, Brun AC, Greibrokk TS, Jacobsen D, Fossum C. [Methemoglobinemia--causes, diagnosis and treatment]. *Tidsskr Nor Laegeforen* 2000;120:1549-1551.
5. Lee SW, Lee JY, Lee KJ, Kim M, Kim MJ. A case of methemoglobinemia after ingestion of an aphrodisiac, later proven as dapsone. *Yonsei Med J* 1999;40:388-391.
6. Southgate HJ, Masterson R. Lessons to be learned: a case study approach: prolonged methaemoglobinaemia due to inadvertent dapsone poisoning; treatment with methylene blue and exchange transfusion. *J R Soc Health* 1999;119:52-55.
7. Ferguson AJ, Lavery GG. Deliberate self-poisoning with dapsone. A case report and summary of relevant pharmacology and treatment. *Anaesthesia* 1997;52:359-363.
8. Lata S, Wiernikowski A, Janiszewski J. [Acute suicidal poisoning with Dapsone]. *Przegl Lek* 1997;54:204-206.
9. MacDonald RD, McGuigan MA. Acute dapsone intoxication: a pediatric case report. *Pediatr Emerg Care* 1997;13:127-129.
10. Maurer HH. Methods for GC-MS. In: Pflieger K, Maurer HH, Weber A., eds. Mass spectral and GC data of drugs, poisons, pesticides, pollutants and their metabolites, Part 4 ed. Weinheim: Wiley-VCH, 2000:3-241.
11. Bickeboeller-Friedrich J, Maurer HH. Screening for detection of new antidepressants, neuroleptics, hypnotics, and their metabolites in urine by GC-MS developed using rat liver microsomes. *Ther Drug Monit* 2001;23:61-70.

12. Maurer HH, Bickeboeller-Friedrich J. Screening procedure for detection of antidepressants of the selective serotonin reuptake inhibitor type and their metabolites in urine as part of a modified systematic toxicological analysis procedure using gas chromatography-mass spectrometry. *J Anal Toxicol* 2000;24:340-347.
13. Maurer HH, Kraemer T, Kratzsch C, Peters FT, Weber AA. Negative ion chemical ionization gas chromatography-mass spectrometry (NICI-GC-MS) and atmospheric pressure chemical ionization liquid chromatography-mass spectrometry (APCI-LC-MS) of low-dosed and/or polar drugs in plasma. *Ther Drug Monit* 2002;24:117-124.
14. Maurer HH, Kratzsch C, Kraemer T, Peters FT, Weber AA. Screening, library-assisted identification and validated quantification of oral antidiabetics of the sulfonylurea-type in plasma by atmospheric pressure chemical ionization liquid chromatography-mass spectrometry (APCI-LC-MS). *J Chromatogr B* 2002;773:63-73.
15. Maurer HH, Kratzsch C, Weber AA, Peters FT, Kraemer T. Validated assay for quantification of oxcarbazepine and its active dihydro metabolite 10hydroxy carbamazepine in plasma by atmospheric pressure chemical ionization liquid chromatography-mass spectrometry (APCI-LC-MS). *J Mass Spectrom* 2002;37:687-692.
16. Pflieger K, Maurer HH, Weber A, eds. *Mass Spectral and GC Data of Drugs, Poisons, Pesticides, Pollutants and their Metabolites, part 5*. 2nd ed. Weinheim: Wiley-VCH, 2003:in preparation
17. Pflieger K, Maurer HH, Weber A, eds. *Mass Spectral Library of Drugs, Poisons, Pesticides, Pollutants and their Metabolites*. 4th ed. Palo Alto (CA): Agilent Technologies, 2003:in preparation
18. Albrecht K, eds. *Intensivtherapie akuter Vergiftungen*. 1 ed. Berlin: Ullstein Mosby, 1997:
19. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989;4:387-392.
20. Anonymous. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 1999;37:731-751.
21. Reigart JR, Trammel HL, Jr., Lindsey JM. Repetitive doses of activated charcoal in Dapsone poisoning in a child. *J Toxicol Clin Toxicol* 1982;19:1061-1066.
22. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet* 1986;11:299-315.