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Euthanasia: A Challenge for the Forensic Toxicologist

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ABSTRACT: People die daily in the hospital. Mostly, they die because their illnesses were no longer treatable (natural death). Unfortunately, some people die an unnatural death, in particular, as the result of euthanasia. In contrast to the situation in most countries, in the Netherlands euthanasia is accepted by the courts under strict conditions. It can be very difficult for the legal authorities to establish whether a person has died from natural causes or from suicide, euthanasia, or murder. In addition to the pathologist and the lawyer, the toxicologist also has a number of problems in showing whether euthanasia has been carried out. These can consist of the following analytical problems:

(*a*) interactions—the patients involved have frequently been receiving a large number of toxic and nontoxic drugs simultaneously;
(*b*) identification—not all drugs administered are included in general screening procedures;
(*c*) metabolites—a large number of metabolites may have accumulated toward the end of a long therapeutic regimen; and
(*d*) determination—determination of quaternary muscle relaxants and their various metabolites, as well as other drugs, can be problematic.

There are also toxicokinetic problems; because of poor kidney and liver function, low serum albumen, general malaise, and interactions between these factors and other drugs, the kinetics of a given drug can differ from normal. This makes it all the more difficult to determine whether the patient died from an accumulation of medication or from a so-called "euthanetic" drug mixture.

The case report of a 79-year-old man who died as a result of either pneumonia or a high pentazocine blood concentration (2200 μg/L) is discussed as an example of these problems. Using a pharmacokinetic calculation, it can be shown that the patient died as the result of an overdose of pentazocine rather than as a result of normal medication.

KEYWORDS: toxicology, pentazocine, euthanasia, toxicokinetics

Active euthanasia is defined as the provision and administration of drugs leading directly to the ending of the life of a seriously ill patient who has repeatedly and expressly asked his or her doctor to carry out this procedure at a prearranged time. Euthanasia can sometimes be carried out in the Netherlands, in contradiction to the law, in a very seriously ill patient who is suffering unbearably and for whom no further treatment is

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possible, if a large number of very strict measures are carried out beforehand. Euthanasia still remains a punishable act. This does not, however, imply that cases of euthanasia are always prosecuted when brought to the attention of the Public Prosecutor. In such cases, the physician can appeal on the grounds of "emergency." It is precisely in these cases that the findings and reports of the forensic physician and toxicologist can be highly influencial [*1–3*]. In these cases, the question of whether the death was caused by suicide, homicide, permissible euthanasia, illegal euthanasia, or natural causes frequently arises. A large number of problems with regard to analysis, toxicokinetics, and interpretation occur here. These will be discussed in detail below.

Analytical Problems

Interactions

The patients involved in such cases are frequently receiving a large number of medicines simultaneously. A number of these drugs are lethal in themselves. The method of analysis must thus be able to distinguish these drugs adequately from other medicines. In particular, forensically insignificant antibiotics are frequently given in high concentrations, which can overload the chromatogram.

Identification

Many analysts and identification libraries (such as those for mass spectrometry) are not attuned to the types of drugs involved here. For example, we recently found an excessive zidovudin concentration in a patient with acquired immunodeficiency syndrome (AIDS). Further, the question arises of what to do with substances not normally included in our screening procedure, such as insulin, methylatropine, and succinylcholine [*4*].

Metabolites

These patients, who are frequently at the end of a long therapeutic regimen, have sometimes accumulated a large number of metabolites in their systems. Thus, both the parent compound and the active metabolites must be determined for each drug. It is necessary only to think of the dozens of metabolites produced by a phenothiazine antiemetic or tranquillizer to realize the scope of the problem of analytical interactions.

Problems of Determination

The range of the concentration of a substance can be very great indeed. Methotrexate, for example, can be present in serum in concentrations that range from as little as 10 μg/L to as much as 1 000 000 μg/L [*5*]!

Quaternary muscle relaxants are sometimes used in cases of euthanasia. Some, such as atracurium, can be simply determined using high-performance liquid chromatography (HPLC) with fluorescence detection [*6*]. Unfortunately, we discovered that the drug atracurium contains *cis-cis*, *cis-trans*, and *trans-trans* isomers, each exhibiting different pharmacokinetic and possibly different pharmacodynamic behavior. Without derivatization, HPLC is insufficiently sensitive and gas chromatography (GC) is insufficiently specific for the determination of pancuronium and vecuronium (a diquarternary derivative) [*7*]. The problem of the determination of suxamethonium is an even greater challenge.

Toxicokinetic Problems

As has been mentioned, we are primarily concerned with seriously ill patients with multiple-organ disturbances who are frequently in a catabolic state. The kinetic parameters given in the literature have mostly been obtained from healthy young volunteers and from animals or, in special cases, from case reports involving a single overdose. Understandably, these values differ considerably from those in the patients with whom we are concerned. In suicide or murder outside the hospital we are nearly always concerned with physically healthy people with normal kinetic parameters. In probable cases of euthanasia in seriously ill patients, we must differentiate between high blood levels of a given drug as a result of an intended lethal overdose and high blood levels of a given drug as a result of disrupted kinetics due to the clinical status of the patient.

The *distribution* of the drug will differ in these patients because of (possibly, a combination of) such factors as lack of exercise, low protein binding, high or low fluid balance, and poor cardiac function.

The *metabolism* of the drug can be increased or decreased by poor hepatic function or as the result of interaction with other drugs (enzyme inhibition or induction).

The *elimination* of the drug can be sharply reduced by altered metabolism and decreased kidney function. Clearance of the drug can be influenced by dialysis as well. These influences are particularly important because euthanasia can be carried out using a drug which the patient is already receiving for therapeutic purposes. A differentiation must thus be made between natural accumulation of the drug and its metabolites and a single overdose.

Interpretation

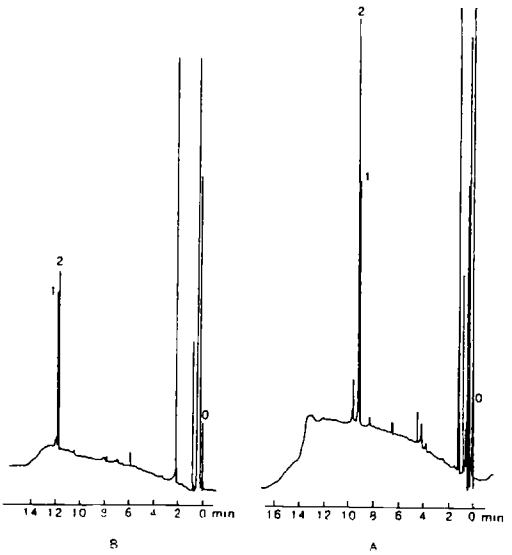
In view of these factors, it is clear that the interpretation of such cases is very difficult. It is difficult to differentiate between death from serious illness and death from overdose. Many questions, some of which are listed below, need to be considered:

1. The differentiation between drug accumulation and a single overdose is even more difficult. Who can, in such cases, make a statement in court "bordering on certainty" which will hold up against an expert lawyer?
2. What do we know about the changes that may take place after death [*8*]?
3. What is known about precisely those drugs used for euthanasia which can be administered intramuscularly, intravenously (slowly or quickly), orally, or rectally?
4. Is it possible that the drug was administered in a normal dose just before death in precisely that vessel from which the blood sample was taken?
5. Which pharmacodynamic interactions are known to occur?

Case History

The following case history will illustrate the problems described above. A 79-year-old, seriously ill, emaciated man died in the hospital after several weeks of intensive treatment. The patient had been admitted to the hospital for treatment of an infection of his hip prosthesis. The man was found to have died from natural causes (pneumonia). The man's daughter thought that he had been poisoned in the hospital and demanded a legal autopsy.

A toxicological examination, following the method of Bouma et al. [*4*], was carried out. Pentazocine was demonstrated in the blood, using the method of Greijdanus and Uges [*9*] (see Fig. 1). This latter method uses capillary gas chromatography with two columns (length, 10 m; internal diameter, 0.32 mm; wall thickness, 0.12 mm; type, Cp-Sil 5 CB and Cp-Sil 19 CB), with a temperature program of 1 min at 100°C, 10°C/min



Capillary GC-chromatogram of pentazocine

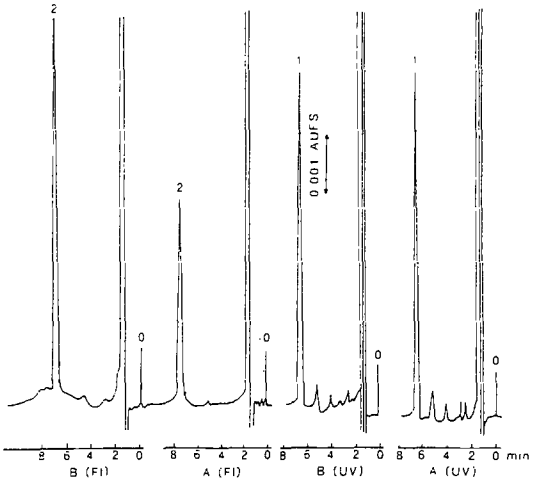
A = Cp-sil 5 CB column, 10 m ; NP/FID
B = Cp-sil 19 CB column, 10 m ; NP/FID
0 = injection
1 = pentazocine (100 μg^{-1} calf's serum)
2 = promazine (internal standard)

FIG. 1—*Capillary gas chromatography chromatogram of pentazocine using two different columns.*

to 230°C, and nitrogen-phosphorus flame ionization detector (NPFID) analysis at 300°C. The detection limit was 5 μg/L of blood. The identify was confirmed using an ion trap detector [electron impact (EI) mode]. The amount of pentazocine was determined with reversed-phase HPLC using the following method: 1 mL of blood, 0.3 mL of buffer at pH 9.6, 0.1 mL of internal standard (0.6 mg promazine per litre of water), 5 mL of a mixture of 98.5% heptane, and 1.5% isoamyl alcohol (v/v) were mixed for 20 min and then centrifuged. The organic layer was extracted using 0.5 mL of hydrochloric acid 0.1 mol/L. The aqueous phase was then mixed with 0.5 mL of buffer at pH 9.0 and 0.1 mL of the 98.5% heptane/1.5% isoamyl alcohol mixture. This solution was then mixed and centrifuged. The amount of 0.06 mL of the upper layer was decanted onto a 5-μm Partisil HPLC column measuring 150 mm by 3 mm in inside diameter. An eluant composed of 10 mL of methanol, 90 mL of dichloromethane (DCM), and 0.15 mL of acetate buffer at pH 3.2 was run through the column at 1 mL/min. An ultraviolet (UV) detector at 254 nm [0.001 absorption units on full scale (AUFS)] and a fluorescence detector (excitation, 278 nm; emission, 310 nm) were used (see Fig. 2). The detection limit with the UV detector was 5 μg/L blood; the coefficient of variation was 3.7%; and the correlation curve from 0 to 2500 μg/L was $r = 0.9999$. The reference and control standards were made using calf's serum [*10*].

Therapeutic antibiotic concentrations (1.1 mg/L of gentamicin) were found in the blood using fluorescence polarization immunoassay (TDx, Abbott Laboratories, Irving, Texas).

Pentazocine was found in concentrations of 2205 μg/L in femoral blood and 30 μg/g



HPLC chromatogram of pentazocine

A = pentazocine calf's serum standard 100 μg l^{-1}

B = serum of a patient on pentazocine 187 μg l^{-1}

UV = UV detection 245 mm

FI = fluorescence detection exc. 278, emi. 310 nm

0 = injection

1 = promazine (internal standard)

2 = pentazocine

FIG. 2—*HPLC chromatogram of pentazocine using a UV and a fluorescence detector.*

in the liver. The reference values for this centrally working analgesic drug are the following [*11–13*]:

Therapeutic serum concentrations, 50 to 200 μg/L
Toxic serum concentration, 1000 μg/L
Possible lethal blood concentrations, 1000 to 2000 μg/L
Postmortem liver concentrations, 3 to 200 μg/g (mean, 35 μg/g)

In 1988, we found a blood concentration of 1600 μg/L in the blood of a 17-year-old boy who was found dead on the street with an empty pentazocine container belonging to his father.

According to Clarke, the ratio of the concentration of pentazocine in serum to that in whole blood is ±0.93 [*11*]. The formula for the age-related clearance, in millilitres per minute [*12*], is

$$\text{clearance} = 29.115 - 0.227 \times \text{age} \times \text{weight}$$

The kinetic data for pentazocine [*12*] are the following:

		20 to 50 Years Old	50 to 90 Years Old
Apparent volume of distribution,	L/kg	4.7 ± 1.2	4.3 ± 2.0
Clearance,	mL/min/kg	22.1 ± 4.1	11.7 ± 3.6
Area under the curve,	mg/L/kg	0.38 ± 0.15	0.78 ± 0.38
Half-life in serum,	h	2.5 ± 0.7	4.1 ± 1.2

Discussion

Because of the pentazocine concentrations found, from a toxicological standpoint, we felt that we had to draw the conclusion that the patient most probably had died of a pentazocine overdose. This conclusion was strengthened by the fact that the pathologist had, at autopsy, found no clear cause of death. The man's chart showed that he had received 30 mg of pentazocine intramuscularly three times a day for seven days. Using a computer program (Mediware, Software for Health Care, Science Park, Groningen, The Netherlands, 1988), we simulated the maximum serum concentration achievable with this dosage, assuming that clearance was half the normal value. The maximum value found was 200 μg/L, with a minimum of 50 μg/L. We then determined the clearance at which the patient could build up the actual blood concentration of pentazocine at the dosage given over a period of seven days. This would have been possible only if the clearance was virtually zero (0.02 mL/min) (Fig. 3). Thus, the overdose could not have been the result of accumulation from the prescribed dose.

Conclusions

From this case, the following conclusions can be drawn:

1. Despite the lack of historical or clinical evidence, an overdose could have been given.
2. Despite the lethal concentrations of the drug, the possiblity exists that the patient died of natural causes.
3. Kinetic simulations can assist in determining whether a given concentration is due to accumulation or to overdose. The conclusions reached in this manner can be wrong if they are based on an interpretation of the analytical results without sufficient knowledge of these factors:
   (*a*) the background of the case,
   (*b*) the postmortem findings, and
   (*c*) the pharmacokinetic, pharmacodynamic, and toxicological properties of the compounds.
4. Normal screening procedures can be insufficient for this type of examination.
5. The toxicologist is not the person who can determine who gave the overdose to the patient—that is, whether it was the patient himself or herself (suicide), the

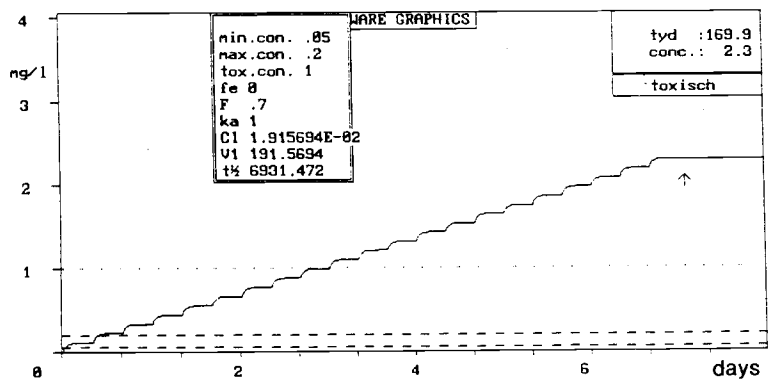


FIG. 3—*Computer plot of the kinetics of pentazocine used to calculate the plasma clearance for a patient taking 30 mg of pentazocine orally three times a day for seven days to reach a final blood concentration of 2200 μg/L. The clearance was calculated to be 0.019 mL/min.*

physician (acceptable euthanasia), the nurse (illegal euthanasia), or the family (murder). His toxicological and kinetic knowledge can contribute to the solution of this type of problem.

Cases of euthanasia will, however, always remain a challenge for the forensic scientist.

References

[1] Merx, C. H. J., "De Dood in Medisch en Juridisch Perspectief," *Nederlands Forensische Tijdschrift,* Vol. 7, No. 1, 1988, pp. 2–7.

[2] Buyze, F, "De Lijkschouwer en de Dood in Het Ziekenhuis," *Nederlands Forensische Tijdschrift,* Vol. 7, 1988, pp. 8–10.

[3] Uges, D. R. A., "How to Interpret the Unexpected Analytical Results of a "Common" Euthanasia Case," *Proceedings,* 23rd International TIAFT Meeting, B. Heyndricky, Ed., Ghent, Belgium, 1986, pp. 191–197.

[4] Bouma, P., Greijdanus, B., Bloemhof, H., IJmker, J., and Uges, D. R. A., "Forensic Toxicological Screening: A Combination of Analytical Techniques," *Proceedings,* 25th Annual TIAFT Meeting, D. R. A. Uges and R. A. de Zeeuw, Eds., Groningen, The Netherlands, 1989, pp. 411–412.

[5] Crom, W. R., Taylor, R. H., and Pratt, C. B., "Methotrexate: Therapeutic Use and Serum Concentration Monitoring," *Individualizing Drug Therapy,* Vol. 1, W. J. Taylor and A. L. Finn, Eds., Gross, Townsend, and Frank, Inc., New York, 1981, pp. 150–173.

[6] Uges, D. R. A., Bloemhof, H., and Agoston, S., "The Determination of Atracurium and Its Main Metabolite Laudanosine in Serum by HPLC," *Pharmaceutisch Weekblad Scientific Edition,* Vol. 6, 1984, p. 265.

[7] Uges, D. R. A. and Bloemhof, H., "Determination of Quarternary Neuromuscular Blocking Agents in Serum by HPLC," *Proceedings,* 21st International TIAFT Meeting E. N. Dunnett and K. J. Kimber, Eds., Brighton, United Kingdom, 1984, pp. 303–308.

[8] Prouty, R. W. and Anderson, W. H., "Postmortem Redistribution of Drugs," *Proceedings,* 24th International TIAFT Meeting, G. R. Jones and P. P. Singer, Eds., Banft, Canada, 1987, pp. 1–21.

[9] Greijdanus, B. and Uges, D. R. A., "Methods for the Analysis of Some Xenobiotics in Body Fluids: VII. Pentazocine," *Ziekenhuisfarmacie,* Vol. 4, 1988, pp. 105–111.

[10] Uges, D. R. A., "The Utility of Lyophilized Spiked Serum as Standard in Clinical and Forensic Toxicological Analysis," R. A. A. Maes, Ed., *Topics in Forensic and Analytical Toxicology,* Elsevier Science Publishers, Amsterdam, 1984.

[11] *Clarke's Isolation and Identification of Drugs,* 2nd ed., Pharmaceutical Press, London, 1986, pp. 860–861.

[12] Garriott, J. C. and Di Maio, V. J. M., "Death in the Dental Chair: Three Drug Fatalities in Dental Patients," *Journal of Toxicology and Clinical Toxicology,* Vol. 19, 1983, pp. 987–995.

[13] Uges, D. R. A., "Reference Values for Clinical-Pharmaceutical and Toxicological Determinations," *Pharmaceutisch Weekblad,* Vol. 122, 1987, pp. 163–181.

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