

Marja-Leena Kortelainen,¹ M.D.

Drugs and Alcohol in Hypothermia and Hyperthermia Related Deaths: A Retrospective Study

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ABSTRACT: Hypothermia and hyperthermia related cases recorded for the period 1973 to 1984 were collected from the files of the Department of Forensic Medicine, University of Oulu, and the necropsy protocols including toxicological results were analyzed. The fact that similar alcohol concentrations were found in both types of fatalities points to the poikilothermic effect of alcohol in humans, as found in animal studies. Both types of deaths seem to be associated with the alcohol elimination phase. Antidepressants and neuroleptics were most often found in the hypothermia cases, but benzodiazepines were also quite frequently present. In spite of the diminished use of barbiturates, these still appear in hypothermia fatalities. Certain other drugs that affect thermoregulation were also noted in solitary cases. Extended toxicological analysis was seldom made in the cases of hyperthermia deaths, and no firm conclusions on the poikilothermic effect of psychotropic drugs could be reached, for example. Therapeutic drug concentrations did not alone predispose the subjects to hypothermia, but appeared in connection with alcohol consumption or chronic diseases.

KEYWORDS: pathology and biology, toxicology, death, alcohol, hypothermia, hyperthermia, drugs, urinary catecholamines

Thermoregulation is affected by a variety of pharmacological agents and is sometimes involved in forensic science cases. Alcohol and certain psychotropic drugs have long been known to play a role in hypothermia deaths [1], and occasionally one also sees hyperthermia cases in which alcohol is not the only pharmacological agent found. It is a common finding that the "sauna deaths" recorded in Finland are often connected with alcohol consumption [2], while in other parts of the world phenothiazides and some other psychotropic drugs have been reported to cause fatal heatstroke during heatwaves [3].

There is a large body of experimental and clinical data available on the hypothermic effect of alcohol on both animals and humans at different degrees of cold exposure [4]. Blood alcohol concentrations in hypothermia deaths are usually reported to be more than 0.15% [5]. Myers [6] has demonstrated that the same dose of ethanol can cause both hypothermia and hyperthermia depending on the ambient temperature, thus rendering an organism poikilothermic. This is probably also true of neuroleptic drugs, for example, chlorpromazine [5].

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¹Assistant doctor in forensic medicine, Department of Forensic Medicine, University of Oulu, Oulu, Finland.

Some authors have reported that barbiturates are a relatively common finding in hypothermia deaths [5], and other drugs such as benzodiazepines and metaqualone have also been mentioned occasionally [1]. It is said that the danger of hypothermia is probably minimal when a drug is taken at normal therapeutic doses [7], although chlorpromazine, for example, has been reported to cause hypothermia even in small doses [5]. On the other hand, the prognosis for cases of hypothermic drug intoxication is quite good as the hypothermia provides protection against hypoxic tissue damage [7].

In addition to drugs and alcohol, some people who die in a state of hypothermia or hyperthermia are suffering from illnesses, mainly cardiovascular or brain diseases. Thus the disease and the drugs used to treat it both predispose the subject to the risk of fatality at abnormal ambient temperatures.

The aim of this retrospective study was to answer the following questions:

1. What is the role of drugs other than alcohol in hypothermia and hyperthermia deaths?
2. Are the same drugs found in both hypothermia and hyperthermia fatalities? In other words, can certain drugs be regarded as poikilothermic in forensic science material, and are there any toxicological findings characteristic of both types of deaths? Also, do therapeutic doses entail a risk in this respect?

Material and Methods

All cases in which hypothermia or hyperthermia was the basic or contributing cause of death were collected from the files of the Department of Forensic Medicine, University of Oulu for the period 1973 to 1984. In these cases blood or urinary alcohol concentrations or both were usually measured. In addition to these determinations, routine drug screening and in some cases also carbon monoxide (CO) or other analysis was made depending on the circumstances of death. Urinary catecholamines, norepinephrine (NE), and/or epinephrine (E) were measured in a part of the hypothermia cases to show a stress response to cold, as described earlier by Hirvonen and Huttunen [8]. The urinary catecholamines had been measured by a fluorometric method up to 1984 [8] and thereafter by liquid chromatography [9].

Number of Cases

Sixty-four hypothermia cases were found, comprising forty-six in which it was considered to be the basic cause of death and eighteen in which it was the contributory factor, including three drownings. Twenty-six hyperthermia cases were found, sixteen of which involved heat-stroke as the basic cause of death and ten as the contributing cause. Where hypothermia or hyperthermia was a contributing factor, the main cause of death was usually either an illness or intoxication.

The manner of death in the hypothermia cases was usually accidental (48 cases), but the material also contained 5 natural deaths and 4 suicides. In 7 cases the manner of death was undetermined. The hyperthermia deaths were also usually accidental (18 cases), but included 7 natural deaths and 1 suicide (Table 1).

Age and Sex

Most of both the hypothermia and hyperthermia cases were males. There were only 10 female hypothermia victims and 5 hyperthermia victims compared with 54 male hypothermia and 21 male hyperthermia victims.

Most of the male hypothermia cases were in the age group 30 to 59 years old and the hyperthermia cases were predominantly in the range 40 to 59 years old. The youngest hyperthermia victim was a 35-year-old male. The female hypothermia victims belonged to nearly all age groups, whereas all 5 female hyperthermia victims were over 60 years old (Table 2).

TABLE 1—*Hypothermia and hyperthermia as basic causes of death or contributing factors. Manner of death.*

	Hypothermia Cases	Hyperthermia Cases
Basic cause of death	46	16
Contributing factor	18	10
Manner of death		
Accident	48	18
Suicide	4	1
Natural	5	7
Undetermined	7	0

TABLE 2—*Age and sex of hypothermia and hyperthermia victims. Number of cases.*

Age Group, years	Hypothermia Victims		Hyperthermia Victims	
	Female	Male	Female	Male
0-10	0	0	0	0
11-20	1	3	0	0
21-30	1	5	0	0
31-40	1	13	0	1
41-50	1	14	0	6
51-60	2	10	0	6
61-70	1	6	1	6
71-80	0	3	4	2
80	3	0	0	0
Total	10	54	5	21

Results

Blood and Urinary Alcohol Concentrations

The mean blood alcohol concentration in the hypothermia deaths was $0.14 \pm 0.13\%$. Blood alcohol at least had been determined in all cases except 1, and the resulting series of 63 cases was found to contain only 20 (31.7%) in which no alcohol was present.

Blood alcohol was measured in all except 2 of the hyperthermia cases, 20 being found to have consumed some alcohol and 4 none. The average blood alcohol concentration was $0.14 \pm 0.10\%$.

Urinary alcohol had been identified in 25 hypothermia cases out of the 42 in which it was measured (59.5%), the mean concentration being $0.21 \pm 0.19\%$. Among the hyperthermia deaths, urinary alcohol determinations had been performed in 16 cases and alcohol was found in all of them, the average concentration being $0.21 \pm 0.13\%$ (Tables 3 and 4).

Extended Toxicological Analysis

An extended toxicological analysis had been carried out for 49 hypothermia deaths (76.6%), in which alcohol was found in 29 cases (59.2%), being the only positive toxicological finding in 17 (34.7%). In 12 cases some other drug was found together with alcohol (24.5%), and in 8 cases (16.3%) some other drug was the only positive finding. In 5 cases (10.2%) neither alcohol nor any other drug was found. The drug-positive findings are listed in Table 5.

TABLE 3—*Blood alcohol concentrations in hypothermia and hyperthermia related deaths.*

Blood Alcohol Concentration, %	Number of Hypothermia Cases	Number of Hyperthermia Cases
0.000	20	4
0.000-0.050	1	2
0.051-0.100	5	1
0.101-0.150	9	1
0.151-0.200	8	8
0.201-0.250	11	4
0.251-0.300	4	3
0.301-0.350	2	1
0.351-0.400	2	0
>0.400	2	0
Total	64	24
Mean \pm standard deviation	0.14 \pm 0.13%	0.14 \pm 0.10%

TABLE 4—*Urinary alcohol concentrations in hypothermia and hyperthermia related deaths.*

Urinary Alcohol Concentration, %	Number of Hypothermia Cases	Number of Hyperthermia Cases
0.000	17	0
0.000-0.050	0	1
0.051-0.100	0	2
0.101-0.150	1	1
0.151-0.200	1	1
0.201-0.250	6	2
0.251-0.300	3	3
0.301-0.350	1	5
0.351-0.400	6	0
>0.400	7	1
Total	42	16
Mean \pm standard deviation	0.21 \pm 0.19%	0.21 \pm 0.19%

TABLE 5—*Drugs found in hypothermia related deaths.*

Drug	Number of Cases with a Positive Finding	Drug with Alcohol	Drug without Alcohol
Benzodiazepine	6	3	3
Antidepressant	5	3	2
Barbiturate	5	2	3
Neuroleptic	5	2	3
Salicylate	4	3	1
Aminophenazon	2	2	0
Caffeine	1	1	0
Lithium	1	0	1

Toxicological analysis was carried out in 13 cases of death from hyperthermia (50%). Drug-positive results were obtained in 6 cases, including 1 subject who had consumed 3 drugs. The drugs are listed in Table 6. A drug alone (without alcohol) was found in 4 cases.

All except one of the hypothermia deaths in which therapeutic doses of drugs without detectable amounts of alcohol were regarded as contributing causes of death involved a disease as another contributory factor, usually diabetes mellitus, fibrosis of the cardiac muscle, schizophrenia, or some other psychosis, or microcerebria. Coronary arteriosclerosis, schizophrenia, and parkinsonism were documented in connection with the hyperthermia deaths involving therapeutic doses of drugs with no alcohol consumption.

Drugs Mentioned in Police Records or Hospital Files

A drug other than alcohol was mentioned in only 20 hypothermia cases, that is, in about one third. The most commonly mentioned drugs are listed in Table 7.

In the hyperthermia cases, a drug other than alcohol was mentioned by name only 11 times, although a comment on the possible existence of some kind of medication was included in 21 cases (almost all). The most commonly mentioned drugs are again listed in Table 7.

Urinary Catecholamines in Hypothermia Deaths

The average urinary NE concentration was 312.7 ± 316.8 ng/mL and the E concentration 111.3 ± 146.2 ng/mL. The mean total catecholamine concentration was 258.0 ± 279.7 ng/mL (Table 8). There were no correlations between blood/urinary ethanol concentration and/or urinary NE/E or total urinary catecholamines (Table 8). The correlations were calculated by regression analysis. In ten cases the total urinary catecholamines were relatively low, less than 70 ng/mL, which is not indicative of hypothermia death. All these victims were heavily or moderately influenced by alcohol and in one of them salicylamide was found. For three of these victims the exposure time was known to be relatively short and the ambient temperature very low.

TABLE 6—*Drugs found in hyperthermia related deaths.*

Drug	Number of Cases with a Positive Finding	Drug with Alcohol	Drug without Alcohol
Caffeine	1	1	0
Neuroleptic (levomepromazine, thiorhidazine)	2	0	2
Barbiturate (mebumale, pentymale)	2	1	1
Chloroquine	1	0	1
Orphenadrine	1	0	1
Digoxine	1	0	1

TABLE 7—Number of cases in which drugs were named in police records or hospital files in hypothermia and hyperthermia cases (excluding alcohol).

Drug	Hypothermia	Hyperthermia
Neuroleptic	9	
Barbiturate	5	
Antidepressant	6	
Benzodiazepine	9	
Mebroamate	1	
Disulfirame	1	
Digitalis	4	3
Vasodilator	2	
Anticholinergic drug	3	
Ergot-alkaloid	1	
Beta blocker	2	
Adrenergic agonist	1	1
Diuretic	2	3
Analgetic (euphoric)	2	
Analgetic (not euphoric)	2	
Corticosteroid	1	
Alsalt (antacid)	1	
Mixture containing ethanol	1	
Potassium		1
Quinidine		1
Insulin		1
Oral diabetes drug		1
Orphenadrine		1
Antihistamine		1
Cimetidine		1
Antibiotic		1
Antithrombotic drug		1
Nitroglycerine		1

TABLE 8—Urinary norepinephrine (NE) and epinephrine (E) in hypothermia deaths and their correlation with blood/urinary alcohol concentrations.

NE, ng/mL	E, ng/mL	Total Catechols, ng/mL	
312.7 ± 316.8 (n = 16)	111.3 ± 146.2 (n = 13)	258.0 ± 279.7 (n = 34)	
	<i>r</i> ^a	<i>p</i> ^a	
Blood alcohol/NE	-0.220	0.632	NS ^a
Blood alcohol/E	-0.156	0.543	NS
Urinary alcohol/NE	0.214	0.510	NS
Urinary alcohol/E	-0.462	0.150	NS
Blood alcohol/total catechols	-0.234	0.179	NS
Urinary alcohol/total catechols	-0.191	0.562	NS

^a*r* = correlation coefficient, *p* = *p* value, and NS = not significant.

Discussion

Blood and Urinary Alcohol Concentration

Blood and urinary alcohol concentrations were practically the same in the hypothermia and hyperthermia related deaths, suggesting that ethanol also seems to be a poikilothermic drug in humans. Thus the same ethanol concentrations can be dangerous in both cold and warm environments. The average urinary alcohol concentrations were a little higher than the blood concentrations in both types of fatalities, indicating that death usually takes place during the alcohol elimination phase. One third of the hypothermia victims had not consumed any alcohol, whereas almost all the hyperthermia victims were under the influence of alcohol. This difference might be due to the greater number of hypothermia cases studied here, or to the more extreme circumstances regarding cold exposure.

Urinary Catecholamines as Indicators of Hypothermic Stress

Although Hirvonen and Huttunen [8] observed increased urinary catecholamine concentrations in hypothermia deaths, with epinephrine more abundant than norepinephrine, the present study, which includes some of the same material, shows NE to be more abundant. The high standard deviations in both NE and E concentrations, and also the total catecholamine concentrations, suggest that the severity of cold stress, and thus the stress response, must be affected by many factors. In three cases alcohol and low ambient temperature together probably led to a rapid death from hypothermia without any significant signs of extreme stress.

Alcohol and Other Drugs

Extended toxicological analysis showed that alcohol was the most common drug found in both types of cases but certain other drugs were also present. Unfortunately, the full toxicology could not be checked in all the hypothermia and hyperthermia related deaths, and consequently these results are not entirely representative.

A drug other than alcohol was the only positive finding in a relatively low number of hypothermia related cases, but the drugs appeared more often with alcohol or in combinations of two or more drugs. Psychotropic drugs were the most common finding in this group. As expected, antidepressants and neuroleptics were to be found, in common with the wealth of experimental and clinical data on their hypothermic effect [10,11].

Benzodiazepines were also present in some hypothermia cases, but did not alone predispose any subject to hypothermia in this material. There is not much experimental or clinical information available on the role of these minor tranquilizers in severe hypothermia, but some evidence has been obtained that they may also have a slight effect on thermoregulation [12,13].

Barbiturates are still occasionally seen in connection with hypothermia deaths, although their clinical use has diminished. This points to potent thermoregulatory effects.

There are also some experimental data on the hypothermic effect of salicylates in afebrile subjects [14], and the present material includes four hypothermia cases in which these drugs were found. Some clinical observations similarly exist regarding the hypothermic effect of lithium together with diazepam [15]. Lithium was the only positive finding in one of the present autopsies. Caffeine is also known to affect thermoregulation, producing hyperthermia in rats [16] and hypothermia at larger doses [17].

Sporadic use of neuroleptics and barbiturates, and also caffeine, chloroquine, orphenadrine, and digoxine, was seen in the present hyperthermia fatalities, whereas no benzodiazepines or antidepressants were found. The number of cases examined was so low, however,

that no firm conclusions can be reached regarding the poikilothermic effect of these drugs, for instance.

Role of Diseases Versus Drugs in the Fatalities

There is no doubt that cardiovascular diseases and brain diseases are of major importance in both hypothermia and hyperthermia deaths. Thermoregulatory mechanisms decrease in efficiency with age, and together with chronic diseases, this impairs the subjects tolerance of abnormal ambient temperatures.

Chronic alcohol abuse and psychiatric disorders are perhaps the most interesting pathological states that can affect thermoregulation themselves or in conjunction with a pharmacological agent. In addition to their potentially dangerous effects in inducing acute drug consumption, they can also promote chronic consumption and this way alter neurotransmission or directly affect the thermoregulatory effector mechanisms. Therapeutic doses of drugs did not seem to predispose any subjects to hypothermia death in this material, but were associated with alcohol or chronic disease.

Conclusion

A complete toxicological analysis should be carried out whenever hypothermia or hyperthermia is suspected to have something to do with a death, and the victim's medical history should be carefully examined and documented to obtain more information on the role of various drugs in fatalities connected with human thermoregulation. This should be emphasized especially with hyperthermia cases, where current toxicological data seem to be insufficient.

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Address requests for reprints or additional information to
Marja-Leena Kortelainen, M.D.
University of Oulu
Department of Forensic Medicine
Kajaanintie 52 D, 90220 Oulu 22
Finland