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Citalopram concentrations in samples from autopsies and living persons

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Abstract Concentrations of citalopram in medicolegal samples from 92 autopsies and 27 living persons are described. In autopsy cases in which citalopram alone was the cause of death, concentrations ranged from 2.0 to 6.2 mg/kg whole blood. In autopsy cases in which citalopram together with other substances was considered to be the cause of death, the concentrations of citalopram ranged from 0.6 to 5.2 mg/kg whole blood. In autopsy cases toxic concentrations ranged from 0.4 to 0.9 mg/kg whole blood and therapeutic concentrations from 0.03 to 0.6 mg/kg whole blood. In samples from living persons the concentrations of citalopram in whole blood were 0.02 to 0.3 mg/kg.

Key words Citalopram · Fatal concentrations · Toxic concentrations · Therapeutic concentrations · Metabolites

Introduction

Citalopram belongs to the second generation of antidepressants and was registered in Denmark in 1989. It is a selective serotonin reuptake inhibitor (SSRI) without cardiovascular adverse effects [1]. It has a half-life of approximately 1½ days, is rapidly absorbed with maximal drug levels in plasma attained within 2 h and has an averaged clearance value of 0.43 l/min by hepatic metabolism (85%) and renal excretion (15%). The distribution volume is between 12–16 l/kg [2, 3]. Only little information on citalopram in forensic cases exists in the literature and as citalopram is manufactured by a Danish company, we found it of interest to make a survey on the occurrence of citalopram in medico-legal cases in Denmark with a population of 5.2 million.

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Materials and methods

The survey includes medicolegal cases examined in Denmark during the period 1989–1996 (autopsies and living persons). Autopsies and toxicological analyses were performed at the Institutes of forensic medicine in Copenhagen, Aarhus and Odense respectively. The analyses of samples from living persons were performed at the Institute of forensic medicine in Copenhagen.

In autopsy cases screening of liver tissue was performed by liquid/liquid extraction followed by capillary gas chromatography using a nitrogen-phosphorous detector (NPD). A secondary confirmation test was done by thin layer chromatography (TLC) or liquid chromatography (HPLC) depending on which of the three laboratories performed the analyses. If citalopram was detected, whole blood was analysed using HPLC and secondary confirmation was done by GC/NPD or GC/MS. If no blood was available muscle tissue was examined as the concentrations are of the same order [4]. In cases involving living persons urine samples were screened after treatment with glucuronidase as described for liver.

The citalopram concentrations found in this investigation were defined as therapeutic for concentrations found in living persons under treatment with citalopram, toxic where concentrations were higher than therapeutic concentrations but not fatal, and fatal for concentrations found in fatal cases in which citalopram was estimated to be the only cause of death.

Results

Citalopram was found in 92 autopsy cases including 50 females and 42 males aged 26–91 years with a median age of 46. Figure 1 shows the distribution during the survey period.

Table 1 shows the median, mean and range of the whole blood concentrations of citalopram in the autopsy cases in which blood was available (n = 86) and in the cases involving living persons. The autopsy cases were divided into four groups in which citalopram was the only cause of death (n = 4), one group in which citalopram together with other compounds was the cause of death (n = 21),

one group with toxic concentrations (n = 18) and one group with therapeutic concentrations (n = 49). In six of the autopsy cases only muscle tissue was analysed as no blood was available. In one of the autopsy cases no citalopram was found in blood whereas 0.4 mg/kg was found in muscle tissue and 2.8 mg/kg in liver tissue.

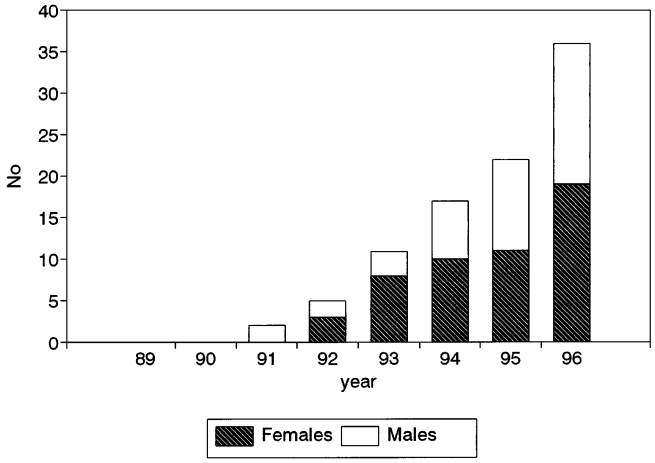

Fig. 1 Number of autopsy cases with citalopram in Denmark (population 5.2 million) 1989–1996

Table 1 Median, mean and range of citalopram concentrations in whole blood in autopsy cases and from living persons

	No of cases	Median (mg/kg)	Range (mg/kg)	Mean (mg/kg)
Autopsy cases				
Fatal				
citalopram alone	4	3.7	2.0–6.2	3.9
citalopram + other	20	0.8	0.6–5.2	1.2
Toxic	16	0.5	0.4–0.9	0.5
Therapeutic	46	0.2	0.03–0.6	0.2
Living persons	27	0.06	0.02–0.3	0.08

The citalopram concentrations from the autopsy cases are shown in Table 2 together with citalopram metabolite concentrations for cases in which these were analysed. Table 2 A shows blood, muscle and liver tissue concentrations of citalopram from cases in which citalopram was the only cause of death and from cases in which citalopram was considered to have contributed to death.

In the four cases in which citalopram alone was considered the cause of death the blood alcohol concentration (BAC) was zero in three cases and was not determined in the fourth case. Three of these cases were considered to be suicides and one accidental/suicide. Of the 21 cases in which citalopram together with other drugs was the cause of death the BAC was zero in 17 of the cases and ranged from 0.84 to 2.50 mg/g in 4 cases. Of the 21 cases 8 were suicides, 8 were accidental and in 5 cases the cause of death was unknown.

In the 18 autopsy cases with toxic concentrations of citalopram the BAC was zero in 8 cases, between 1.42 and 3.43 mg/g in 8 cases and not determined in 2. Of the cases 2 were suicides, 10 were considered to be accidental and the cause of death was unknown in 6 of the cases (Table 2 B).

In the 49 autopsy cases with therapeutic concentrations of citalopram, the BAC was zero in 24 cases, less than 1.00 mg/g in 9 cases, from 1.00 to 3.20 mg/g in 15 cases, and not determined in 1 case. Of the cases 10 were suicides, 4 accidental/suicides, 27 accidental (Table 2 C), 7 unknown and 1 was homicide by gunshot. In one of the cases no citalopram was found in the blood, but the muscle tissue was found to contain 0.4 mg/kg and the liver tissue 2.8 mg/kg.

The results from the 27 living persons are shown in Table 3 including 10 females and 17 males aged 20–67 years with a median age of 42 years. Of these cases 20 concerned traffic violations, 3 acts of violence and in

Table 2 Autopsy cases with A) citalopram alone or citalopram with other compounds the cause of death, B) toxic concentrations of citalopram and other causes of death than citalopram, C) therapeutic concentrations of citalopram and other causes of death than citalopram

Cause of death	Material	Citalopram		Desmethyl-citalopram		Didesmethyl-citalopram	
		mg/kg	no of cases	mg/kg	no of cases	mg/kg	no of cases
A:							
Citalopram alone	blood	2.0–6.2	4	5.0	1	0.9	1
	liver	24–55	2	50	1	–	
Citalopram + other	blood	0.6–5.2	20	0.1–0.9	11	0–0.1	9
	muscle	4.2	1	–		–	
	liver	1.9–36	14	0.7–13	10	0–3.0	3
B:							
	blood	0.4–0.9	16	0.03–0.2	11	0–0.09	9
	muscle	0.4–0.8	2	–		–	
	liver	1.1–16	15	0.3–14	12	2.7	1
C:							
	blood	0.03–0.6	46	0.0–0.2	25	0.0–0.03	21
	muscle	0.06–0.7	4	–	–	–	–
	liver	0.4–21	34	0.0–3.7	24	0.06–0.9	7

Table 3 Concentrations of citalopram and metabolites in whole blood from living persons

Material	Citalopram		Desmethyl-citalopram		Didesmethyl-citalopram	
	mg/kg	no of cases	mg/kg	no of cases	mg/kg	no of cases
Whole blood	0.02–0.3	27	0.0–0.3	26	0–0.21	26

4 cases no information was available. The BAC was zero in 6 cases, from 0.01 to 0.99 mg/g in 8 cases, 1.10 to 3.10 mg/g in 9 cases and was not determined in 5 cases. Other drugs were present in 21 of the cases and 3 of the cases were analysed for citalopram only. In three of the cases no other drugs were found present, but in all three cases the BAC was higher than 2.00 mg/g.

Discussion

Very little information on citalopram concentrations in overdose cases exists in the literature. Lindegaard Pedersen et al. [1] described a patient who took an overdose of citalopram resulting in levels about 6 times higher than the average therapeutic level but no signs of severe toxicity were seen. In particular no changes occurred in consciousness, electrocardiogram or blood pressure. Neuvonen et al. [5] described three cases, in which citalopram was involved. In two of these cases 1.7 and 0.5 mg citalopram/kg blood was found respectively and these concentrations were considered to be 5 and 2 times higher than the therapeutic level. In the third case a concentration of 0.3 mg/kg blood was found which was considered therapeutic. Moclobemide was found in very high concentrations in all three cases and in all of the cases the cause of death was considered to be a central serotonin syndrome. The citalopram concentrations in the first two cases are in agreement with our findings, whereas the concentration in the third case is in the area between therapeutic and toxic concentrations in our investigation. We did not find moclobemide in any of the cases examined in this study.

Öström et al. [6] found citalopram concentrations in the range from 5.2 to 49 mg/kg in blood from six suicides where no other causes of death were found.

Alcohol was not found in any of our cases with fatal concentrations of citalopram whereas in the cases with toxic or therapeutic citalopram concentrations high alcohol concentrations were found quite often.

Comparing the therapeutic citalopram whole blood concentrations from the autopsy cases with those from the living persons, the concentrations were found to be slightly higher in the autopsy cases which could be due to post mortem alterations.

Lindegaard Pedersen et al. [1] and Overø [2] found mean plasma concentrations of 0.08 mg/kg after a daily intake of 40 mg citalopram. Baumann [7] found plasma concentrations from 0.04 to 0.3 mg/kg after a daily intake of 30–60 mg citalopram but reported large individual variations in the plasma concentrations and that desmethylcitalopram retains a pronounced serotonergic profile. The concentration of this metabolite is therefore relevant even though Lindegaard Pedersen et al. [1] stated that it has a lower potency than the main compound. Cases in which didesmethylcitalopram was determined in this investigation showed very low concentrations of this metabolite. In forensic cases, however, the co-determination of metabolites is important in order to obtain the clearest picture possible.

Citalopram does not seem to posses any pronounced sedative effect. However, Lindegaard Pedersen et al. [1] found a distinct hypersomnic effect in some of their patients. This effect might explain the cause of death in four of the cases in the present investigation in which the only findings were citalopram in toxic or therapeutic concentrations together with alcohol. Probably lower concentrations of citalopram may cause death if combined with the intake of alcohol. Steentoft et al. [8] described a similar effect for morphine and alcohol.

In the suicide cases in which only citalopram was found, the blood concentrations were 10 times higher than therapeutic concentrations. This indicates that citalopram possesses a low toxicity range when used correctly.

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References

1. Lindegaard Pedersen O, Kragh-Sørensen P, Bjerre M, Overø KF, Gram LF (1982) Citalopram, a selective serotonin reuptake inhibitor: clinical antidepressive and long-term effect – a phase II study. Psychopharmacology (Berl) 77:199–204
2. Overø KF (1982) Kinetics of citalopram in man; plasma levels in patients. Prog Neuropsychopharmacol Biol Psychiatry 6:311–318
3. Kragh-Sørensen P, Overø KF, Lindegaard Pedersen O, Jensen K, Parnas W (1981) The kinetics of citalopram: single and multiple does studies in man. Acta Pharamcol Toxicol 48:53–60
4. Christensen H, Steentoft A, Worm K (1985) Muscle as an autopsy material for evaluation of fatal cases of drug overdose. J Forensic Sci Soc 25:191–206
5. Neuvonen PJ, Pohjola-Sintonen S, Tacke U, Vuori E (1993) Five fatal cases of serotonin syndrome after moclobemide-citalopram or moclobemide-clomipramine overdoses. Lancet 342:1419
6. Öström M, Eriksson A, Thorson J, Spigset O (1996) Fatal overdose with citalopram. Lancet 348:339
7. Baumann P (1992) Clinical pharmacokinetics of citalopram and other selective serotogenic-reuptake inhibitors (SSRI). Int Clin Psychopharmacol 6:13–20
8. Steentoft A, Worm K, Pedersen CB, Sprehn M, Mogensen T, Sørensen MB, Nielsen E (1996) Drugs in blood samples from unconscious drug addicts after the intake of an overdose. Int J Legal Med 108:248–251