Letter to the Editor

Significance of Bile Analysis in Drug-Induced Deaths*

To the Editor:

Most studies examining the biological distribution of drugs have reported the analyses in blood, liver, brain, and urine (1). Very few studies have reported data on bile. Closer examination of some of these publications revealed that bile had significantly higher concentrations of drugs than blood in almost all cases reported, yet bile is not commonly used as a specimen in routine toxicological analysis. The following is a summary of some of the cases from the literature that reported bile concentrations in addition to blood concentrations. Data for barbiturates and opiates were not included. All three benzodiazepines listed in Table I showed significantly higher concentrations in bile than in blood (2,3). In half of the cases involving diazepam, bile concentrations were even higher than liver concentrations.

In the case of antidepressant drugs (Table II), all drugs showed several-fold higher concentrations in bile than in blood. Drugs such as doxepin, imipramine, trimipramine, sertraline, and norsertraline showed higher concentrations in bile than in liver. For several antidepressant drugs, only one case was found in the literature that reported bile concentrations in addition to blood concentrations, and it is being presented here as such (2,4–9).

All the drugs listed in Table III, including chlorpromazine, thioridazine, ethchlorvynol, methapyrilene, methaqualone, and phenmetrazine, had higher bile concentrations than blood concentrations (2,10–20). In the case of ethchlorvynol, methaqualone, isoniazid, acebutolol, metoprolol, mexiletine, and phenmetrazine, bile concentrations were higher than the liver concentrations. For several of these drugs, only one case was found in the literature that reported bile concentrations in addition to blood concentrations.

Data obtained from the Medical Examiner's Office on cocaine and three of its metabolites (ecgonine methyl ester, benzoylecgonine, and cocaethylene) are presented in Table IV. In all the cases analyzed, bile concentrations were higher than the blood concentrations for the parent drug, cocaine, as well as for all the metabolites. Liver concentrations were not available. An average of 50 cases indicated that cocaine was present in bile in amounts approximately five times higher than in blood. Ecgonine methyl ester was approximately three times higher than in blood. The average bile concentration of benzoylecgonine was approximately six times higher

Table I. Distribution of Benzodiazepines in Bile, Blood, and Liver

Analyte drug	No. of cases	Bile concentration* (mg/L)	Blood concentration* (mg/L)	Liver concentration* (mg/L)
Chlordiazepoxide	2	4.0 (1.0–7.0)	2.5 (1.0–4.0)	5.5 (1.0–10)
Diazepam	4	2.8 (0.7–6.0)	0.9 (0.4–1.3)	2.1 (1.2–3.0)
Flurazepam	3	43 (30–64)	8.9 (5.5–11)	52 (9.0–130)

* Average (range).

Table II. Distribution of Antidepressant Drugs in Bile, Blood, and Liver

Analyte drug	No. of cases	Bile concentration* (mg/L)	Blood concentration* (mg/L)	Liver concentration* (mg/L)
Amitriptyline	23	25 (0.3–171)	2.2 (0.1–17)	27 (0.1–323)
Amoxapine	1	61	18	150
Desipramine	3	39 (18–67)	5.6 (1.2–8.0)	48 (22–87)
Dothiepin	3	65 (12–157)	3.0 (0.9–7.4)	–
Doxepin	3	108 (81–148)	7.4 (1.9–11)	60 (6.7–95)
Fluoxetine	1	0.013	0.006	–
Imipramine	15	45 (1.7–171)	3.7 (0.3–10)	39 (1.3–140)
Maprotiline	1	161	6.2	–
Norsertraline	14	57 (0.1–236)	0.4 (0.02–3.0)	9.4 (0.4–42)
Nortriptyline	1	11	2.0	–
Sertraline	14	11 (0.2–35)	0.3 (0.02–1.3)	5.1 (0.1–34)
Trazodone	1	45	15	57
Trimipramine	1	2.4	1.3	1.8

* Average (range).

*This study was presented in part at the 33rd International Congress on Forensic and First on Environmental Toxicology (GRETOX 1995) held in Thessaloniki, Macedonia, Greece in August 1995.

Table III. Miscellaneous Drugs in Bile, Blood, and Liver

Analyte drug	No. of cases	Bile concentration* (mg/L)	Blood concentration* (mg/L)	Liver concentration* (mg/L)
Acebutolol	1	416	22	123
Chlorpromazine	3	80 (11–200)	1.37 (0.5–2.0)	115 (6.0–190)
Chlorprothixene	1	3.9	0.1	–
Diltiazem	1	180	11	–
Ethchlorvynol	8	382 (2.5–2000)	78 (1.3–180)	217 (1.8–620)
Flecainide	2	290 (160–419)	53 (13–94)	365 (180–550)
Isoniazid	1	900	43	650
Methapyrilene	2	25 (21–29)	8.05 (7.1–9.0)	34 (22–45)
Methaqualone	2	83 (40–125)	8.1 (8.0–8.3)	30 (25–36)
Methylphenidate	1	5.7	2.8	2.1
Metoprolol	1	254	4.7	6.3
Mexiletine	1	440	38	190
Phenmetrazine	6	4.37 (0.5–19)	0.78 (0.10–2.0)	4.23 (0.3–20)
Thioridazine	1	9.0	3.0	35

* Average (range).

Table IV. Distribution of Cocaine and Its Metabolites in Bile and Blood

Analyte drug	No. of cases	Bile concentration* (mg/L)	Blood concentration* (mg/L)
Benzoylecgonine	50	12 (0.18–59)	2.43 (0.06–26)
Cocaethylene	13	0.55 (0.39–3.68)	0.08 (0.0–6.44)
Cocaine	50	0.73 (0.02–6.13)	0.15 (0.02–2.18)
Ecgonine methyl ester	50	3.30 (0.11–18)	1.21 (0.07–9.66)

* Average (range).

than its average blood concentration. Cocaethylene was found in bile in amounts seven times higher than in blood. It must be noted that, in several cases, cocaethylene was found negative in blood but was present in bile. This further emphasizes the need to analyze bile as a routine toxicological specimen. If bile samples had not been analyzed, the presence of cocaethylene in several cases would have been missed.

From the information presented here, it is apparent that a routine analysis of bile could prove useful because most drugs are found in bile in significantly higher amounts than in blood. More importantly, those cases in which a drug is not present in blood may not be considered negative for that drug unless a biliary analysis is also performed. A drug present in low concentrations in a system may go undetected if blood is the only specimen analyzed. There is a much smaller chance of this happening if bile is also analyzed. It should also be noted that bile concentrations in several cases were higher than liver concentrations. It has been argued that the presence of drugs in bile indicates only long-term usage. This may be true in cases of acute poisoning, where only a short time has elapsed between drug administration and death and where the drug was not distributed to the tissues. However, in most of the drug distribution cases reported in the literature that also reported data on bile, bile concentrations were higher than the blood concentrations.

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