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# AN AUTOPSY CASE OF POISONING WITH SELECTIVE SEROTONIN REUPTAKE INHIBITOR, PAROXETINE

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## Abstract

A female in her twenties was found dead in her room. She had received medications for depression and panic disorder, and had attempted suicide several times. Many packets of prescribed drugs, including paroxetine, were found near the corpse. At autopsy, the lungs were edematous. The organs were slightly congested with putrefactive change. Autolytic rupture, considered as gastromalasia, was observed in the anterior cardiac portion of stomach wall. Toxicological examination revealed 0.78, 3.20 and 17.63 μg/ml of paroxetine in the heart blood, femoral blood and urine, respectively. Acetaminophen and phenobarbital were also identified within therapeutic or sub-lethal levels. Taking into consideration postmortem diffusion of drugs, we evaluated postmortem data and concluded that the death was mainly due to toxicity of paroxetine with serotonin syndrome.

**Key words:** Paroxetine – Poisoning – Postmortem diffusion

## Souhrn

### Pitevní nález otravy selektivním inhibitorem zpětného vychytávání serotoninu (paroxetin)

Dvacetiletá žena byla nalezena mrtvá ve svém pokoji. Byla medikamentózně léčena pro depresivní a panické poruchy, a opakovaně se pokoušela o suicidium. V blízkosti těla bylo nalezeno mnoho balení předepsaných léčiv, včetně paroxetinu. Při pitvě byly plíce edematózní. Orgány vykazovaly známky mírné kongesce a změny způsobené rozkladem. Autolýzou způsobená ruptura, označená jako gastromalacie, byla popsána na přední části stěny žaludku v oblasti kardie. Toxikologické vyšetření stanovilo 0,78, 3,20 a 17,63 μg/ml paroxetinu v kardiální, respektive femorální krvi a v moči. Acetaminophen a phenobarbital byly také stanoveny, a to v terapeutické či subletální koncentraci. Autoři vyhodnotili údaje získané post mortem, při čemž vzali v úvahu posmrtnou difuzi léků a došli k závěru, že smrt byla způsobena toxicitou paroxetinu spolu se serotoninovým syndromem.

**Klíčová slova:** paroxetin – otrava – difuze post mortem

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## INTRODUCTION

Mood disorders (e.g. major depressive disorder and panic disorder) are thought to be associated with heterogeneous dysfunction of biogenic amines. It is suggested that depression results from a functional deficit of either serotonin or norepinephrine at the receptor site in the central nervous system [4, 10]. Tricyclic antidepressants (TCAs) have classically been prescribed for these disorders. Unfortunately, these have poor selectivity for monoamine transporter inhibition, undesirable side effects and significant toxicity [5].

In recent years, selective serotonin reuptake inhibitors (SSRIs) have been widely prescribed as first-line agents instead of TCAs [10]. Paroxetine, (-)-(3S, 4R)-4-(4-fluorophenyl)-3-[(3, 4-methylenedioxy) phenoxymethyl] piperidine, is one of the SSRIs used as an antidepressant. It has very mild anti-cholinergic effects, no activity on histamine or @1-adrenergic receptors, and its main metabolites have no pharmacological properties [13]. For these reasons, poisoning with paroxetine is rarely reported compared with other psychiatric drugs [5, 14].

Here, we report a case of poisoning with paroxetine probably accompanied by serotonin syndrome.

### Case history

A female in her twenties (153 cm, 47 kg) was found dead in her room with many empty packets of prescribed drugs. Her body was discovered in a prone position. She had been suffering from depression and panic disorder, and was prescribed multiple medications including 30 mg daily of paroxetine. She had a history of several suicide attempts and self-injury. Three days before her corpse was found, she was hospitalized for overdose with acetaminophen-containing drugs and discharged on the next morning.

At autopsy, hesitation mark scarring on her left wrist was the only external injury observed. Putrefactive discoloration of skin was also noted. Both lungs (left 290 g, right 355 g) were

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**Tab. 1. Drug concentrations in each sample (μg/ml) and their fatal and therapeutic levels**

| | Paroxetine | Acetaminophen | Phenobarbital | Promethazine | Chlorpromazine | Nitrazepam |
|---|---|---|---|---|---|---|
| Heart blood | 0.78 | 25.96 | 9.25 | N.D. | N.D. | N.D. |
| Femoral blood | 3.20 | 45.35 | 9.44 | N.D. | N.D. | N.D. |
| Urine | 17.63 | 219.97 | 4.38 | N.D. | N.D. | N.D. |
| Peritoneal fluid | 42.43 | 35.63 | 12.68 | 2.13 | 3.12 | 0.95 |
| Therapeutic levels | 0.031–0.062 | 10–20 | 10–40 | 0.006–0.099 | 0.01–0.50 | 0.03–0.1 |
| Fatal levels | > 0.41< | > 160 | > 80 | 2.4-12 | 3-12 | > 5 |
| References | [5] | [15] | [15] | [15] | [15] | [11] |

7-aminonitrazepam, a metabolite of nitrazepam, was not detected from each specimen. N.D.: Not detected.

edematous and 300 ml of pleural effusion was observed in the thoracic cavities. The brain had no macroscopic abnormality. The heart (220 g) had no lesions such as atherosclerosis, myocardial fibrosis or anatomical abnormalities. It contained 150 ml of blood with chicken fat clots. Both the anterior cardiac portion of stomach and lower portion of esophagus were autolytic, considered as gastromalacia [7], and approximately 80 ml of dark brownish peritoneal fluid was present. The bladder contained approximately 150 ml of slightly yellow clear urine. Organs showed putrefactive changes and were slightly congested. The postmortem interval was speculated to be approximately two days.

Drug screening using Triage® (Biosite Diagnostic Inc, San Diego, USA) was positive for barbiturates. In microscopic examination, all tissues showed postmortem changes. Lungs were edematous and liver showed centrilobular eosinophilic change.

**Toxicological examination**

Subsequent toxicological examination was performed using a high performance liquid chromatography drug analysis system (Class-VP system, Shimadzu, Kyoto, Japan), operated in accordance with the manufacturer's specifications [6]. Toxicological analysis identified paroxetine, acetaminophen and phenobarbital in blood and other specimens (Table 1). In addition to these drugs, peritoneal fluid contained chlorpromazine, promethazine and nitrazepam.

No ethanol was detected from blood or urine using headspace gas chromatography.

## DISCUSSION

The incidence of adverse effects associated with SSRIs is reported to be small compared with conventional TCAs. The lowest concentration at which death was attributed to paroxetine alone was reported to be 0.41 μg/ml [5]. In this case, the concentrations of paroxetine in the heart and femoral blood exceeded fatal levels (Table 1). While, blood concentrations of phenobarbital and acetaminophen were within therapeutic or sub-lethal levels [15]. The femoral/heart blood concentration ratio of paroxetine, acetaminophen and phenobarbital were 4.10, 1.75 and 1.02, respectively. These elevated concentrations in femoral blood may be due to postmortem diffusion from urine or peritoneal fluid. Relatively high concentrations of urinary paroxetine and acetaminophen in the bladder could accelerate drug diffusion into the femoral vein [8].

Paroxetine is a substrate for and a potent inhibitor of cytochrome P450 (CYP) 2D6, and a weak inhibitor of CYP3A4 [5, 10, 13]. This inhibition can suppress the metabolism of paroxetine itself and other drugs. In the present case, microscopic analysis of the liver showed centrilobular eosinophilic changes suggesting paroxetine metabolism was reduced by hepatocytic damages. These mechanisms may extend the biological half-life and lead to elevation of paroxetine blood concentration to lethal levels.

SSRIs increase serotonin concentration in the synaptic cleft by inhibiting presynaptic serotonin reuptake [10]. This serotonin overstimulation produces a constellation of symptoms called serotonin syndrome [1, 5, 10, 13]. It results from not only the combined use of SSRIs and monoamine oxidase inhibitors but also from SSRI monotherapy [2, 9]. The syndrome is characterized by a "clinical" triad of mental-state changes, autonomic hyperactivities (e.g. hyperthermia) and neuromuscular abnormalities [3, 12]. As the rectal temperature of the corpse decreased to environmental temperature and antemortem symptoms were unclear in present case, serotonin syndrome could not be diagnosed. However, it is strongly speculated that the deceased suffered from serotonin syndrome due to an excessive intake of paroxetine.

From the autopsy findings and the results of toxicological examination, we concluded that death was mainly due to paroxetine toxicity, with possible partial contribution from acetaminophen and phenobarbital. We took into consideration the postmortem diffusion of drugs when evaluating the postmortem data.

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# ZPRÁVY ZE SJEZDŮ

## DVADCAŤ ROKOV OSTEUROPAVEREIN RECHTSMEDIZIN

Osteuropaverein Rechtsmedizin – Východoeurópsky spolok súdneho lekárstva je súčasné označenie pre inštitúciu, ktorá vznikla pri Nemeckej spoločnosti súdneho lekárstva pôvodne ako „Spolok na podporu spolupráce so súdnymi lekármi z východnej a južnej Európy". Spolok bol založený pani Dr. B. Kühnholz, súdnou lekárkou, pôsobiacou v tom čase na Inštitúte súdneho lekárstva v Kieli a ďalšími 14 kolegami dňa 20. 09. 1989 v Salzburgu v Rakúsku. Pani Dr. Kühnholz sa stala zároveň aj prvou prezidentkou novovzniknutého spolku. Spolok sa hodlal zaoberať podporou vedy a výskumu v oblasti súdneho lekárstva a tým prispieť k umožneniu výmeny výsledkov výskumu medzi západo- a východoeurópskymi krajinami.

Tento cieľ mal byť dosiahnutý hlavne tým, že mladé kolegyne a kolegovia, v tom čase ešte zo socialistických európskych štátov, budú pozývaní do Nemecka na výročné súdnolekárske dni a tým dôjde k zlepšeniu spolupráce medzi vedcami z východu a západu. Na súdnolekárske dni mali byť pozývané kolegyne a kolegovia, ktorí by aspoň sčasti ovládali nemecký jazyk a mali byť finančne podporovaní – zaplatením kongresových poplatkov a ubytovania počas kongresu. Jedinou podmienkou bolo prihlásenie príspevku – prednášky alebo posteru – venovaného problematike, ktorou sa vo svojej práci zaoberajú.

Len niekoľko týždňov po založení spolku došlo k revolúcii v strednej a východnej Európe, k pádu berlínskeho múru a neskôr aj k znovuzjednoteniu Nemecka. Tým sa vytvorili predpoklady pre podstatné zlepšenie spolupráce a to vďaka získanej slobode v cestovaní pre kolegov, ktorí sa mohli ľahšie dostať do Nemecka. Ostávalo vyriešiť problém financovania spoluúčasti zahraničných kolegov na výročných dňoch Nemeckej spoločnosti súdneho lekárstva. Vďaka príspevkom vedúcich Inštitútov ako aj ďalších súdnych lekárov bolo možné každý rok pozývať viaceré kolegyne a kolegov. Počet kolegov, ktorí mohli byť spolkom každoročne podporovaní, sa zvyčajne pohyboval medzi 10 až 20. Kolegyne a kolegovia prichádzali z Poľska, Českej republiky, Slovenska, Estónska, Lotyšska, Litvy, Maďarska, Slovinska, Rumunska, Bulharska, Ruska, Bieloruska a Macedónska. Na tieto aktivity naviazali neskôr návštevy nemeckých kolegov v týchto krajinách a ich účasť na tamojších národných kongresoch.

Medzičasom sa väčšina spomínaných krajín stala členmi Európskej únie a tým zároveň začalo obdobie novej kvality spolupráce. Počas dvoch rokov sa uskutočnili pod záštitou Východoeurópskeho spolku súdneho lekárstva dve medzinárodné sympóziá. V roku 2007 bolo v Prahe 1. sympózium na tému „Týranie a zneužívanie dieťaťa" organizované prof. Bouškom a Dr. Kurtom Trübnerom, súčasným prezidentom Východoeurópskeho spolku, ktorý na tomto poste po dlhých rokoch práce nahradil pani Dr. Kühnholz. V roku 2008 bolo v rámci 1. slovensko-českého vedeckého zjazdu súdneho lekárstva organizované 2. sympózium v Gabčíkove – Dr. Šidlo, opäť za spoluúčasti Dr. Trübnera, na tému „Organizácia a úlohy súdneho lekárstva".

Dúfame, že tieto kontakty medzi súdnymi lekárkami a lekármi našich krajín sa budú naďalej zlepšovať a tým bude aj Európa v oblasti súdneho lekárstva spoločne rásť.

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