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# ANALYSIS OF ACUTE CLONAZEPAM INTOXICATIONS DURING THE TEN-YEAR PERIOD 2001 – 2010

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In the article acute intoxications by clonazepam (Rivotril) consulted with the National Toxicological Information Centre (NTIC) in Bratislava during the years 2001 – 2010 are analysed. 431 records of acute clonazepam intoxications were evaluated according to gender, age, cause, poisoning severity score and therapy. 57% of all patients were female, 42% were male. The highest number, 123, was in the age between 19 – 35 years and 117 between 36 – 50 years, and most of these cases were suicidal attempts (85% and 90%). Accidental poisoning was most common in children under 5 years of age (65 cases). In the age over 65 years were 4 cases. 69% of all evaluated intoxications were suicidal and 18% were accidental. 61% of intoxications were combined, particularly with alcohol and antidepressant, anxiolytic and antiepileptic drugs. The most common poisoning severity score (68% cases) was PSS 1, which means intoxications accompanied by mild, transient and spontaneously resolving symptoms – fatigue, somnolence, ataxia. There were five lethal cases (PSS 4) as the consequence of combined drug intoxications with suicidal intent. Complete data about therapeutical treatment were obtained for 114 patients. In most cases, hospital treatment was non-specific decontamination and supportive symptomatic therapy. 97 patients received activated charcoal, 55 activated charcoal with laxative, 38 gastric lavage and 12 patients were given the specific antidote flumazenil (Anexate).

By retrospective analysis, we found an increasing tendency of clonazepam intoxications mainly suicidal.

In spite of the fact that it is mandatory to report intoxications to the NTIC in the form of a copy of the medical record of each patient hospitalized due to intoxication, there are still medical facilities which don't fulfil this requirement. If all the medical records were available, it would lead to more precise knowledge about intoxications in Slovakia and a better possibility for introducing measures to lower the number and consequences of intoxication.

***Keywords:****Acute intoxication– Clonazepam– Rivotril – National Toxicological Information Centre*

## INTRODUCTION

According to statistical data of the National Toxicological Information Centre (NTIC) in Bratislava, benzodiazepines were the most frequent cause of drug intoxications up until the year 2005. In 2005, analgesics, mainly ibuprofen and paracetamol, took first place. Of benzodiazepines, clonazepam was the second most abused drug, after alprazolam, in 2009 – 2010. As for drug preparations, Rivotril (with effective substance clonazepam) was the second most abused drug (following Ibalgin) [1,2].

Benzodiazepines bind to $GABA_A$ receptor subtype in the areas of the limbic system, thalamus and hypothalamus. They bind to an allosteric site of the $GABA_A$–$Cl^-$ receptor complex. This action increases the frequency of the opening of the chloride channels. Benzodiazepines enhance the affinity of GABA (gamma-aminobutyric acid) for $GABA_A$ receptors and potentiate the inhibitory effects of GABA throughout the nervous system. The effects of GABA-mediated actions account for benzodiazepines' sedative–hypnotic, anxiolytic, anticonvulsant, and skeletal muscle relaxation properties [3].

In the Slovak Republic, Rivotril is the only one registered preparation with the active ingredient clonazepam. It is available in the form of tablets (0.5 mg and 2 mg of clonazepam in each tablet) and oral drops (2.5 mg/ml). Clonazepam exhibits pharmacological properties which are common to benzodiazepines but anticonvulsive effects are more pronounced. This is beneficial in treatment of generalised and focal epilepsies. Therapeutic indications of clonazepam are all clinical forms of epileptic disease and seizures, especially absence seizures (petit mal); primary or secondarily generalised tonic–clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements [4,5]. Clonazepam is also used for short-term therapy of panic disorder with or without agoraphobia. Anxiolytic effects of clonazepam can be partially explained by upregulation of serotonergic receptors, specifically $5\text{-}HT_1$ and $5\text{-}HT_2$. Other off-label indications are therapy of insomnia and augmentation therapy of acute mania [6–8].

Clonazepam is quickly and completely absorbed after oral administration. Peak plasma concentrations are reached in most cases within 1 – 4 hours. The mean volume of distribution is large; it is estimated at about 3 l/kg. Plasma protein binding is 85%. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk. Within 4 – 10 days, 50 – 70% of the oral dose of clonazepam is excreted in the urine and 10 – 30% in the faeces in the form of free or conjugated metabolites. Less than 0.5% appears as unchanged clonazepam in the urine. The mean elimination half-life is long – about 30 hours (18 – 60h) [4].

Benzodiazepine overdose is associated with relatively low morbidity and mortality. Most deaths associated with benzodiazepines result from mixed overdoses of benzodiazepines and other central nervous system depressants, especially alcohol [8]. Although rare, fatalities are more likely to occur with short-acting benzodiazepines (e.g. triazolam, alprazolam or temazepam). Mild toxicity is characterized by drowsiness, ataxia, motor incoordination, dysarthria (slurred speech), nystagmus, confusion and cognitive impairment. Psychologically, the patient displays different degrees

of paranoia, or erratic behaviour, and is easily aroused. In moderate toxicity, the patient is aroused by verbal stimulation, although he or she may enter coma stage one or two. Patients with severe toxicity are unresponsive except to deep pain stimulation, consistent with coma stage one or two. In general, respiratory depression and hypotension are rare. Screening for benzodiazepine serum concentrations is generally not useful in overdose. Clinical management of acute overdose is symptomatic and may also incorporate the use of a specific antidote flumazenil [3].

## METHOD

Acute intoxications by clonazepam, consulted with the NTIC in the years 2001 – 2010, were retrospectively analyzed from medical and NTIC records. We evaluated the intoxications according to gender, age, cause and poisoning severity score (PSS). We investigated whether the intoxications were caused by clonazepam alone or together with other drugs and evaluated the most frequent therapy.

## RESULTS AND DISCUSSION

During the ten-year period, the NTIC provided 23582 consultations by telephone. Of these, 11082 concerned drug intoxications, 1508 intoxications by antiepileptic drugs and 431 intoxications by clonazepam. Clonazepam intoxications made up 29% of intoxications by antiepileptics and 4% of intoxications caused by all drugs (Fig. 1).

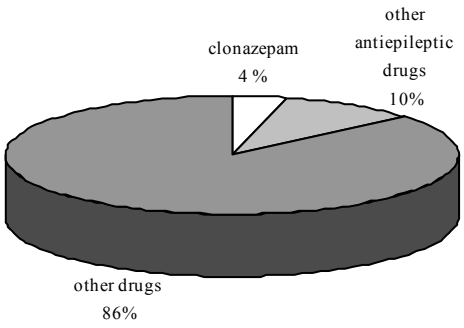


**Figure 1. Drug intoxications consulted in years 2001 – 2010**

During the monitored period, the number of clonazepam intoxications had a rising tendency (Fig. 2). In 2007, there was a sharp increase of recorded cases, which might be caused by the duty to report intoxications to the NTIC since 2006 [9].

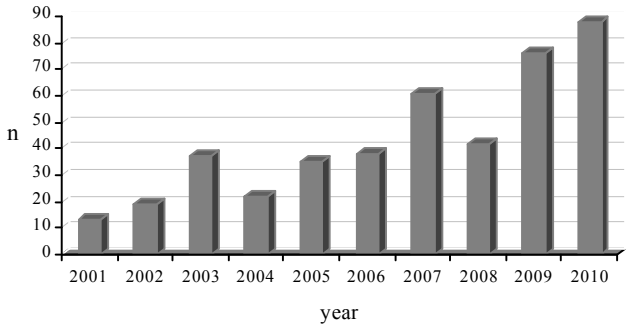


**Figure 2. Number of clonazepam intoxications consulted in years 2001 – 2010**

Of the total number of 431 patients with clonazepam poisoning, 245 were female (57%) and 180 male (42%). In 6 cases, sex was not specified in the records.

Most of the patients (240 i.e. 56%) were between 19 and 50 years old. Detailed age distribution of consulted clonazepam intoxication is in Fig. 3.

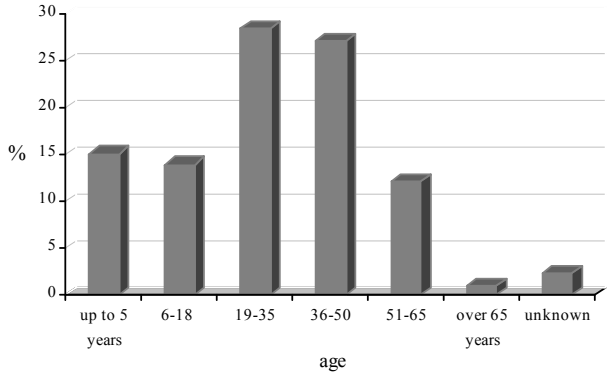


**Figure 3. Clonazepam intoxications consulted in years 2001 – 2010 divided according to age**

Together 69% of intoxications were suicidal and 18% were accidental; 13% were unknown (Fig. 4). The prevailing number of suicidal intoxications could be related to the fact that patients with chronic diseases, mainly epilepsy, have depressive and suicidal tendencies relatively often. The results of numerous studies comparing mortality as a result of suicide among epileptic and healthy patients indicate that epileptic patients have a higher tendency towards suicide.

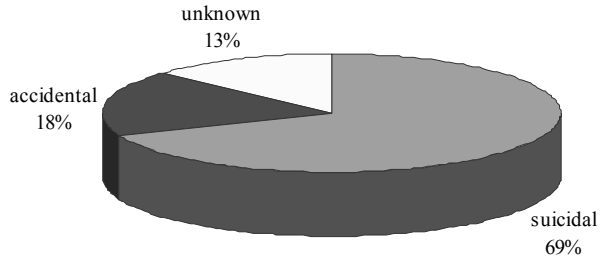


**Figure 4. Clonazepam intoxications consulted in years 2001 – 2010**

According to the literature, suicidal intoxication attempts are more frequent in women and more successful in men [10]. The cases of clonazepam intoxication, which we analyzed, confirmed the first assertion, as the incidence of attempts at suicidal intoxication was markedly higher in women (188) than in men (108). There were 5 recorded deaths – 3 women and 2 men. In the analyzed group of acute clonazepam intoxications, suicidal intoxications prevailed in the age group of adults between 19 – 50-year-olds (209 out of 298 suicidal intoxications), followed by the group of 6 – 18-year-olds (40 cases), then the age group of 51 – 65-year-olds (42 cases), and 3 cases in the age group above 65 years.

Accidental intoxications prevail mainly in children up to 5 years of age [11]. This was also confirmed in our study of acute clonazepam intoxications. Of the total number of 77 recorded accidental poisonings, 59 were in children up to 5-year-olds, 11 cases in the age group of 6 – 18-year-olds, 4 cases in the group of 19 – 50 year olds, 2 cases in the category of 51 – 65 years old and in one case the age was not recorded. In children, the most frequent cause of accidental poisoning were mistakes in dosage or keeping drugs in the reach of children. Intoxications by Rivotril in the form of drops (a clear solution with peach aroma) were frequent.

The poisoning severity score (PSS) enables the qualitative evaluation of intoxication. It is assessed according to the most severe clinical symptom observed. One symptom in any organ system is enough for assignment to a severity score [12]. In most of the intoxications caused by clonazepam (68%) only mild, transient and spontaneously resolving symptoms (PSS 1) occurred. The PSS was most often defined by symptoms pertaining to the CNS: fatigue, drowsiness, anxiety, restlessness, ataxia, mild visual or auditory disturbances (PSS 1), confusion, agitation or unconsciousness with appropriate response to pain (PSS 2) or deep coma unresponsive to pain (PSS 3). 15% of cases were with no symptoms related to poisoning (PSS 0). Some cases were just suspect intoxication; in some cases the symptoms of intoxication were not yet manifested. In some cases gastric lavage was performed, vomiting was induced or activated charcoal was applied sooner than symptoms were manifested. Moderate intoxication with pronounced or prolonged symptoms (PSS 2) was found in 9% of patients, severe or life-threatening symptoms were in 2% of patients and exitus (PSS 4) was found in 5 cases (1.2%). Severe intoxications were mainly sequels

of combination of clonazepam with substances that potentiated the depressive effect on CNS.

Of the total number (431) of clonazepam poisoning cases, 39% were caused by clonazepam alone, while 61% were caused by intoxication by clonazepam in combination with other substances; most commonly in combination with alcohol (41 cases), various anxiolytic antidepressants, antipsychotics or other antiepileptics(Fig. 5).

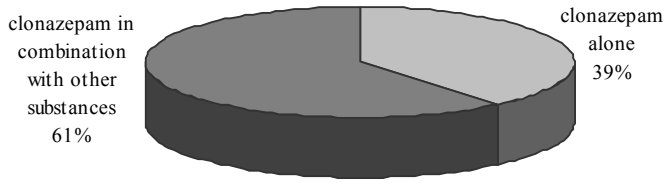


**Figure 5. Clonazepam intoxications consulted in years 2001 – 2010**

On the basis of a professional regulation of the Ministry of Health of the Slovak Republic, which entered into force on June 30th 2006, institutional healthcare providers are required to report cases of intoxication to the NTIC. Reports are sent in the form of a copy of the medical record of the patient who was hospitalized for intoxication.

We found out the therapeutical procedures from the medical records, which were sent to the NTIC from the healthcare facilities where the therapy was provided. This group consisted only of 114 cases, which is only 26.5% of the total number of consulted clonazepam intoxications in the years 2001 – 2010. We recorded the therapy, which was aimed specifically at clonazepam and also in cases of combined intoxication.

In cases of acute clonazepam intoxication NTIC recommends, as a basis, symptomatic and supportive therapy and nonspecific elimination. In cases of serious consciousness damage and after careful consideration of possible contraindications, it is possible to use the specific benzodiazepine antidote – flumazenil (Anexate). Gastric lavage is effective, if done in less than one hour after clonazepam ingestion. Secondary elimination methods, such as forced diuresis, haemodialysis and haemoperfusion are not effective due to the large volume of distribution and high plasma protein binding. Symptomatic and supportive therapy comprises the monitoring of physiological functions – breathing, pulse frequency and blood pressure; infusion therapy, along with general supportive measures securing equipment to eliminate possible failure of breathing. Hypotension can be treated with sympathomimetics (dopamine, noradrenaline) and fluids, and bradycardy with atropine [13]. Nonspecific elimination consists of a single bolus dose of active charcoal (AC; 1g/kg of body mass) or of multiple-dose AC, usually 50g every 4 hours (a total of 200 g), if vomiting is a problem 12.5 g charcoal hourly. AC is most effective when applied immediately after intoxication. Thanks to its huge adsorption surface in powder form (other forms substantially reduce its adsorptive effect), it is today considered as a universal antidote [14]. To speed up the elimination, it is applied with a laxative when necessary.

Nonspecific elimination was the most frequent form of therapy in the group of evaluated clonazepam intoxication. AC was applied in 97 out of 114 analyzed cases, i.e. 85%, of which in 56 cases it was applied with a laxative (49%), most often with lactulose (Duphalac). Gastric lavage was performed in 38 cases. In 4 cases, parents induced vomiting as a pre-hospital first aid.

Flumazenil (Anexate) is a specific competitive inhibitor of substances, which act via the benzodiazepine receptors, specifically blocking their central effects. The hypnotic-sedative effects of the agonist clonazepam are rapidly reversed by flumazenil. In the case of high plasma concentration of clonazepam it is necessary repeat the dose of flumazenil because of its short half-life (1h) [15]. Flumazenil should be applied only in case of a seriously reduced conscious level, but it is often used unreasonably [16,17]. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a tricyclic antidepressant or any other drug that causes seizures. This is because clonazepam may be suppressing seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control. Flumazenil should be used with caution in patients with a history of seizures, head injury or chronic benzodiazepine use (risk of withdrawal syndrome) [18]. Among 114 analysed cases flumazenil was applied 12 times for the treatment of mild intoxications, when the application of the antidote was unnecessary.

## CONCLUSION

By retrospective analysis we found an increasing tendency of clonazepam intoxications, which were mainly caused by a suicide attempt. Suicidal tendencies are more frequent in patients with chronic diseases, especially epilepsy than in the general population [19]. Moreover several studies suggested that treatment with some antiepileptic drugs is associated with the occurrence of symptoms of depression and an increased risk of suicidal thoughts and behaviours. Clinicians should screen all people with epilepsy for suicidality, depression or anxiety disorders and should obtain a family psychiatric history. People with epilepsy must be warned that there is a small increased risk of suicidality associated with some antiepileptics but that the risk of not taking antiepileptics is more substantial [20]. It would be beneficial for patients to cooperate with patients' organizations, where there is a possibility of preventing states leading to suicide attempts.

The incidence of accidental intoxication can be significantly decreased by preventive measures. It is important for drugs to be stored outside the reach of children and for adults not to take drugs in front of children. Drugs in the household should be stored in their original packing; safety closure caps are preferable [11].

In spite of the fact that it is mandatory to report intoxications to the NTIC in the form of a copy of medical record of each patient hospitalized due to intoxication, there are still medical facilities which don't fulfil this requirement. If all the medical records were available, it would lead to more precise knowledge about intoxications in Slovakia and a better possibility for introducing measures to lower the number and consequences of intoxication.

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# ANALÝZA AKÚTNYCH INTOXIKÁCIÍ KLONAZEPAMOM ZA DESAŤROČNÉ OBDOBIE 2001 – 2010

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V práci sú analyzované akútne intoxikácie klonazepamom (Rivotril) konzultované s Národným toxikologickým informačným centrom (NTIC), v Bratislave v rokoch 2001 – 2010. Súbor tvorilo 431 záznamov konzultácií hlásených intoxikácií klonazepamom, ktoré boli hodnotené podľa pohlavia, veku, príčiny (suicidálny pokus, náhoda), stupňa závažnosti intoxikácie a terapie. Z celkového počtu pacientov bolo 57 % žien a 42 % mužov. Najvyšší počet intoxikácií (123) bol zaznamenaný vo vekovej skupine od 19 do 35 rokov a tiež v skupine od 36 do 50 rokov (117), pričom väčšinou išlo o suicidálne intoxikácie (85 % resp. 90 %). Najviac náhodných otráv (65) bolo u detí do 5 rokov. Nad 65 rokov boli zaznamenané 4 intoxikácie. 18 % zo všetkých intoxikácií bolo náhodných a 69 % suicidálnych. Intoxikácie samotným klonazepamom tvorili 39 %. 61 % bolo kombinovaných intoxikácií, hlavne s alkoholom, antidepresívami, anxiolytikami a antiepileptikami. Najčastejšie (68 %) sa vyskytovali mierne intoxikácie (PSS 1). V 5 prípadoch kombinovaných intoxikácií so suicidálnym úmyslom bol stupeň závažnosti PSS 4, t.j. smrteľná intoxikácia. Terapeutické postupy boli vyhodnotené zo 114 prepúšťacích správ pacientov hospitalizovaných kvôli intoxikácii klonazepamom. Prevládala nešpecifická eliminácia a symptomatická a podporná terapia. 97 pacientom bolo podané aktívne uhlie, 55 pacientom aktívne uhlie kombinované s laxatívom, v 38 prípadoch bola vykonaná gastrická laváž a v 12 prípadoch bolo podané špecifické antidotum flumazenil (Anexate). Retrospektívnou analýzou sme zistili stúpajúcu tendenciu intoxikácií klonazepamom, najmä suicidálnych. Napriek tomu, že od roku 2006 je povinné hlásenie intoxikácií NTIC vo forme kópie prepúšťacej správy každého pacienta hospitalizovaného kvôli intoxikácii, sú ešte zdravotnícke zariadenia, ktoré si túto povinnosť neplnia. Ak by boli všetky prepúšťacie správy k dispozícii, znamenalo by to presnejšiu informovanosť o intoxikáciách na Slovensku a lepšiu možnosť zavedenia opatrení na zníženie počtu a následkov intoxikácií.

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