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## Anticoagulant Rodenticides Poisonings in Humans and Animals – Short Review



حالات التسمم بمبيدات القوارض المضادة للتخثر عند البشر والحيوانات - مراجعة قصيرة

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### Abstract

Anticoagulant rodenticides (AR) are among the most commonly used rodent control pesticides. The current second-generation rodenticides in worldwide use are referred to as superwarfarins. These substances have relatively low toxicity to humans but significant toxicity to animals, including pets.

AR work at the level of hepatocytes by blocking the synthesis of plasma coagulation factors II, VII, IX, and X as well as proteins C, S, and Z, resulting in severe coagulation disorders predominant in the clinical picture.

Deaths associated with AR poisoning are the result of haemorrhages into the gastrointestinal tract, peritoneal cavity, or intracranial cavities.

Medico-legal diagnosis of AR poisonings is based on the clinical picture, autopsy, and histopathological and toxicological examinations.

### المستخلص

مبيدات القوارض المضادة للتخثر هي من بين مبيدات الآفات الأكثر استخداماً لمكافحة القوارض. ويشار إلى الجيل الثاني الحالي من مبيدات القوارض المستخدمة في جميع أنحاء العالم باسم الورافيرينات الفائقة. هذه المواد لها سمية منخفضة نسبياً للإنسان ولكنها ذات سمية كبيرة للحيوانات، بما في ذلك الحيوانات الأليفة.

تعمل مبيدات القوارض المضادة للتخثر ARs على مستوى خلايا الكبد عن طريق منع تشييد عوامل تجلط الدم في البلازما وهي II و VII و IX و X وكذلك البروتينات C و S و M و Z ما يؤدي إلى اضطرابات تجلط دم شديدة تتبلور في الصورة السريرية.

وترتبط الوفيات المتعلقة بالتسمم بمبيدات القوارض المضادة للتخثر AR بالنزيف في الجهاز الهضمي أو في التجويف البريتواني أو في التجاويف داخل الجمجمة.

ويعتمد التشخيص الطبي القانوني لحالات التسمم بمبيدات القوارض المضادة للتخثر AR على الصورة السريرية والتشريح وفحوصات الأنسجة والسمية.

**Keywords:** Forensic Science, Anticoagulants, Rodenticides, Poisoning, Humans.

**الكلمات المفتاحية:** علوم الأدلة الجنائية، مضادات التخثر، مبيدات القوارض، التسمم، الإنسان.



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## 1. Introduction

In some parts of the world, poisonings with biocidal compounds are the most common type of poisoning in humans. An important subgroup of this group of compounds are rodenticides. Some countries such as Iran, India, Bangladesh, and Jordan use phosphide derivatives, e.g. aluminium phosphide [1], whereas European countries and the US use anticoagulant rodenticides (AR).

The first AR put on the market was warfarin [2]. After several years of exposure to warfarin, rodents developed almost complete resistance to this compound. This immunity emerged as a monogenic, autosomal dominant trait [2,3]. It became necessary to produce rodenticides to which animals would be susceptible. This led to the synthesis of so-called superwarfarins (second-generation rodenticides). These compounds are divided into indanedione derivatives (chlorphacinone, diphacinone, pindone) and 4-hydroxycoumarins (brodifacoum, difenacoum, bromadiolone, coumatetralyl, flocoumafen, difethialone). In the country of the authors, all second-generation rodenticides as well as warfarin-based rodenticides are available [3], of which the most commonly used are 4-hydroxycoumarin derivatives.

AR poisonings in humans occur most often by the oral route and much less frequently percutaneously in the case of mass exposure (farmers, producers) [4]. Some animals (rabbits, guinea pigs) can absorb a large amount of poison through the skin, which leads to acute poisoning [2]. Once absorbed into the body, AR quickly get into the liver where they bind to hepatocytes. AR inhibit the activity of the vitamin K 2,3-epoxide reductase and thus the gamma-carboxylation process. This results in impaired synthesis of functional plasma coagulation factors II, VII, IX, and X as well as proteins C, S, M, and Z. In addition, there is an increase in the concentration of inactive vitamin K 2,3-epoxide [5]. This effect may persist for a very long time, i.e. for weeks or even months after taking a single dose of poison.

Due to their almost unlimited availability, AR can also be used for other than their original purpose. They are characterized by relatively low acute toxicity to humans; therefore, suicide attempts with their use are usually ineffective. Laszkowska-Lewko et al. [5] reported an unusual case of the use of AR by a female patient with suspected

Munchausen syndrome to self-induce disease symptoms. During the first hospitalization, the patient had nasal bleeding and haematuria with simultaneous indeterminable prothrombin time (PT) (increased international normalized ratio [INR]) and prolonged activated partial thromboplastin time (APTT). Over the course of two years, the patient was hospitalized dozens of times, presenting symptoms of haemorrhagic diathesis (nosebleeds, haemorrhages in the tongue region, numerous ecchymoses, bleeding from the gastrointestinal tract, intramuscular haemorrhages). Laboratory tests revealed prolonged APTT and reduced concentrations of prothrombin, factor VII, factor IX, factor X, and proteins C and S with normal values of factor V. The patient underwent genetic, radiological, and ultrasound testing, computed tomography, magnetic resonance imaging, bone scintigraphy, positron emission tomography, and tumour marker determination. After the last hospitalization in the intensive care unit due to acute respiratory failure and massive haemorrhage of the lower respiratory tract, the authors of this article were consulted. Our analyses using ultra-performance liquid chromatography–photodiode array detection (UPLC-PDA) and liquid chromatography–tandem mass spectrometry (LC-MS/MS) showed the presence of brodifacoum in the blood of the patient at a concentration of 544 ng/ml [5]. AR could be used by in-patients with Munchausen syndrome by proxy. It was described by Babcock et al. [16].

Poisonings with AR are more severe in animals than in humans. This is probably due to the greater sensitivity of animals to this group of chemical compounds. Poisonings in animals are either accidental (eating an attractive-looking food) or intentional (administration of rat poison in sausages or other meat products). Severe anticoagulant rodenticide poisonings in dogs, unlike in humans, most often have an acute or hyperacute course and lead to the death of the animal [4]. Nicpoń et al. reported the case of a dog admitted to the Clinic of Diseases of Horses, Dogs and Cats because of intense haematemesis and persistent bloody diarrhoea. The gastroscopy showed haemorrhagic gastritis and a large amount of blood in the gastrointestinal lumen. At the same time, features of acute toxic liver damage were observed (unlike in humans). The animal died during a



convulsive seizure that did not respond to diazepam. The autopsy showed ecchymoses in mucous membranes and bloody fluid in the peritoneal and pleural cavities, and the pericardial sac. The lumen of the stomach and intestines was filled with a lot of fresh and coagulated blood. Histopathological examination revealed massive congestion of internal organs, blood cell aggregates in blood vessels of the lungs and myocardium, and haemorrhagic hepatic necrosis. Toxicological testing found brodifacoum in blood [3].

Medico-legal diagnosis of AR poisonings is complex and based on several elements: clinical picture and results of laboratory medical diagnostics (hemostasis parameters), autopsy picture, histopathological picture, and toxicological test results (determination of AR in biological samples). The clinical picture, if available to a forensic specialist, is very diverse. In the case of mild poisonings, the only symptoms may be minor nosebleeds or complete absence of pathological symptoms. Moderate poisonings are associated with haemorrhages in mucous membranes, ecchymoses, nosebleeds, bleeding from the upper gastrointestinal tract, haematuria, and haemoptysis. The most serious symptoms include intracerebral haemorrhage and massive bleeding from the genital or respiratory tracts. There have been reports of fatal poisonings accompanied by, among others, bleeding into the pleural cavity (difenacoum poisoning) [6], massive pulmonary haemorrhage (brodifacoum poisoning) [7], and subarachnoid haemorrhage (brodifacoum poisoning) [8]. The clinical picture of AR poisoning can be very ambiguous and resembles leukaemia or infectious diseases such as bacterial sepsis, rickettsioses, plague, and leptospirosis [7]. In clinical laboratory studies, even mild poisonings show an increase in the INR value, while in severe cases, patients develop severe disorders with a deficiency of the prothrombin complex factors (II, VII, IX, X, proteins C, S, Z, M) [2].

The half-life of AR is usually very long, e.g. for brodifacoum it is 56 days, while for bromadiolone it is 3.5 days in the rapid elimination phase and 24 days in the slow elimination phase [10]. Consequently, these substances can be detected in the blood of the patient for many months after poisoning. Olmos et al. described a case of poisoning of a

woman with brodifacoum. The concentration of this compound 5 days after admission was 1.302 ng/ml (determined by high-performance liquid chromatography - HPLC), and the authors observed a gradual decrease in this concentration over the following days. Brodifacoum can be detected in the blood of a patient until 209 days after poisoning [9]. In their study, brodifacoum was determined in biological material with the HPLC method. A similar method with fluorescence detection was used by Palmer et al., who described a case of fatal brodifacoum poisoning in a 15-year-old girl. The highest concentration of brodifacoum was found in bile (4276 ng/ml) and femoral blood (3919 ng/ml); brodifacoum was also found in frozen liver (50 ng/g) and in formalin-fixed liver (820 ng/g). The substance was not found in the vitreous body of the eye [7].

Mass spectrometry-based methods, well-established in forensic toxicology, are also useful in the diagnosis of AR poisonings, e.g. Vindenes et al. developed a method for determining bromadiolone using liquid chromatography-mass spectrometry (LC-MS). In their study, the determined limit of detection (LOD) was 5 ng/ml and the limit of quantification was 10 ng/ml. [11]. Yan et al. used the liquid chromatography-electrospray-tandem mass spectrometry (LC-ESI/MS/MS) technique to determine bromadiolone and brodifacoum with LOD at, respectively, 0.1 ng/ml and 0.2 ng/ml [12]. In their review article, Imran M et al. indicate the possibility of diagnosing AR poisonings with such methods as HPLC coupled with ultraviolet and fluorescence detectors, liquid chromatography-electrospray ionization-tandem mass spectrometry, liquid chromatography with high resolution tandem mass spectrometry, ultra-performance liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry, ion chromatography with fluorescence detection, ion chromatography-electrospray ionization-ion trap mass spectrometry, and ion chromatography-electrospray ionization-tandem mass spectrometry [13]. The toxic concentrations of AR are (in mg/L in blood): 0.1 for chlorophacinone, 0.02 for brodifacoum, 0.5 for difenacoum, 0.12 for coumatetralyl and 0.02 for bromadiolone [17]. It should be kept in mind that a negative result of the toxicological blood test does not rule out poisoning with these compounds. AR rapidly penetrate



hepatocytes, where they cause pathobiochemical changes for many months after poisoning. In that case, blood concentration of AR will be below the LOD.

Thanks to the long half-life of AR, their determination in parts of the liver of birds of prey and water birds allows to assess their exposure to AR and thus determine the impact of these substances on the food chain [14, 15]. The results of Thomas et al. [14] show that livers of great horned owls contain larger amounts of AR residues than the livers of red-tailed hawks, which may be associated with a slightly different diet and occupied territory. This type of research highlights the difficulty in eliminating the risk of exposure to AR of non-target species.

Diagnosis of AR poisoning in animals is based primarily on the clinical picture or, in the case of the death of the animal, on the autopsy or histopathological changes. Laboratory testing does not routinely include coagulation or toxicological tests. Due to the unavailability of advanced analytical methods in veterinary toxicology, determination of AR is usually carried out by thin-layer chromatography (TLC) [3].

## 2. Conclusion

AR poisoning is a problem observed around the world. AR poisoning can be accidental, suicidal or as a result of disease development (Munchausen syndrome). Modern analytical methods used in a toxicology laboratory allow the detection of these substances in biological material, which increases the chances of correct diagnosis of poisoning.

## References

1. Navabi SM, Navabi J, Aghaei A, Shaahmadi Z, Heydari R. Mortality from aluminum phosphide poisoning in Kermanshah Province, Iran: characteristics and predictive factors. *Epidemiol health*. 2018;40:e2018022-. <https://doi.org/10.4178/epih.e2018022>
2. Bennett DL, Caravati EM, Veltri JC. Long-acting anticoagulant injection: a prospective study. *Vet Hum Toxicol*. 1987;27:459-60.
3. Zawadzki M, Magdalan J, Niedźwiedz A. Poisonings with anticoagulant rodenticides. *Arch Med Sad Krym*. 2007;LVII:427-9.
4. Nicpoń J, Zawadzki M, Niedźwiedz A, Kubiak K, Jankowski M, Magdalan J. Anticoagulant rodenticides poisoning in dogs. *Med Wet*. 2007;63(12):1604-6
5. Laszkowska-Lewko M, Rybka J, Zawadzki M, Jurek T, Wróbel T. Coagulation disorders caused by chronic poisoning with anticoagulant rodenticides – case report and review of literature. *Hematol* 2017;8(4):289-92. <https://doi.org/10.5603/Hem.2017.0041>
6. Soubiron L, Hantson P, Michaux I, Lambert M, Mahieu P, Pringot J. Spontaneous haemoperitoneum from surreptitious of a rodenticide. *Eur J Med*. 2000;7:305-7.
7. Palmer RB, Alakija P, de Baca JE, Nolte KB. Fatal brodifacoum rodenticide poisoning: autopsy and toxicology findings. *J Forensic Sci*. 1999;44: 851-5. <https://doi.org/10.1520/JFS14566J>
8. Kruse JA, Carlson RW. Fatal rodenticide poisoning with brodifacoum. *Ann Emerg Med*. 1992;21(3):331-6. [https://doi.org/10.1016/S0196-0644\(05\)80900-X](https://doi.org/10.1016/S0196-0644(05)80900-X)
9. Olmos V, Lopez CM. Brodifacoum poisoning with toxicokinetic data. *Clin Toxicol (Phila)*. 2007;45(5):487-9. <https://doi.org/10.1080/15563650701354093>
10. Lo VM, Ching C, Chan AYW, Mak TWL. Bromadiolone toxicokinetics: diagnosis and treatment implications. *Clin Toxicol (Phila)*. 2008;46(8):703-10. <https://doi.org/10.1080/15563650701504366>
11. Vindenes V, Karinen R, Hasvold I, Bernard JP, Morland JG, Christophersen AS. Bromadiolone poisoning: LC-MS method and pharmacokinetic data. *J Forensic Sci* 2008; 53(4): 993-6. <https://doi.org/10.1111/j.1556-4029.2008.00737.x>
12. Yan H, Xiang P, Zhu L, Shen M. Determination of bromadiolone and brodifacoum in human blood using LC-ESI/MS/MS and its application in four superwarfarin poisoning cases. *Forensic Sci Int*. 2012;222(1-3):313-7. <https://doi.org/10.1016/j.forsciint.2012.07.008>
13. Imran M, Shafi H, Wattoo SA, Chaudhary MT, Usman HF. Analytical methods for determination of anticoagulant rodenticides in biological samples. *Forensic Sci Int*. 2015;253: 94-102. <https://doi.org/10.1016/j.forsciint.2015.06.008>
14. Thomas PJ, Mineau P, Shore RF, Champoux L, Martin



- PA, Wilson LK, Fitzgerald G, Elliott JE. Second generation anticoagulant rodenticides in predatory birds: Probabilistic characterization of toxic liver concentrations and implications for predatory bird populations in Canada. *Environ Int.* 2011;37:914-920. <https://doi.org/10.1016/j.envint.2011.03.010>
15. Lambert O, Pouliquen H, Larhantec M, Thorin C, L'Hostis M. Exposure of raptors and waterbirds to anticoagulant rodenticides (difenacoum, bromadiolone, coumatetralyl, coumaten, brodifacoum): epidemiological survey in Loire Atlantique (France). *Bull Environ Contam Toxicol.* 2007;79:991-4. <https://doi.org/10.1007/s00128-007-9134-6>
16. Babcock J, Hartman K, Pedersen A, Murphy M, Alving B. Rodenticide-induced coagulopathy in a young child. A case of Munchausen syndrome by proxy. *Am J Pediatr Hematol Oncol.* 1993;15:126-30. <https://doi.org/10.1097/00043426-199302000-00021>
17. Schulz M, Iwersen-Bergmann S, Andersen H, Schmoldt A. Therapeutic and toxic blood concentrations of nearly 1000 drugs and other xenobiotics. *Crit Care.* 2012;16(4): R136. <https://doi.org/10.1186/cc11441>

