Canine status epilepticus due to acute intoxication*

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Key words
Poisoning, case series, dog, epilepsy, organophosphates, carbamates, metaldehyde, criminidine, strychnine, zinc phosphate

Summary
Objectives: The purpose of this study was to describe the type of toxin ingested, clinical presentation and outcome of dogs with status epilepticus (SE) due to acute poisoning presented to a large referral veterinary hospital. Materials and methods: Retrospective case series. Medical records of all dogs suffering from SE were reviewed (Jan 1, 2002 to April 30, 2009). Results: Fourteen dogs with SE due to acute intoxication were identified. Toxicological analyses (qualitative analysis with gas chromatography/mass spectrometry; n = 11) detected poisonings with carbofuran, criminidine, paraoxon, metaldehyde, strychnine and diazinon. In the other three cases the uptake of a known poison was observed (zink phosphate, metaldehyde). None of the dogs showed evidence of neurological disease up to the day of presentation. The dogs were hospitalised for 2–10 days (median 5 days). The survival rate was 85.7%. None of the dogs experienced any more seizures after discharge (median observation period 2.6 years). Conclusion and clinical relevance: Ancillary to the acute clinical presentation, preliminary reports (possible uptake of poisonous material) and an inconspicuous medical history may suggest a tentative diagnosis. Managed adequately, these patients can have a high survival rate.Clinicians should also keep uncommon intoxications in mind.

Introduction
As in humans, seizure disorders are a common presentation of neurological disease in dogs (1, 33). Usually, epileptic seizures (ES) are categorised as idiopathic, symptomatic or reactive ES. When no underlying cause of the seizure disorder can be found and a genetic predisposition is assumed in dogs younger than 5 years with a normal interictal neurological examination, the term idiopathic epilepsy is used (3, 27). If a structural disease of the brain causes ES, the term symptomatic or secondary epilepsy is used. The third etiological group, reactive ES, originates from the response of a healthy brain to a transient systemic disorder (endogenous metabolic diseases or exogenous poisonings) (2, 33).

General epilepsy (GE) represents the condition in which the cause of the seizures is not known. As in humans, primary ES (idiopathic ES) is the term used to describe these situations (3, 27). Secondary ES reflects ES in which there is a known underlying cause (8). In veterinary medicine, ES, the term symptomatic or secondary epilepsy is used.

Canine status epilepticus (SE) due to acute intoxication was diagnosed in 14 dogs (1, 33). The purpose of this study was to describe the type of toxin ingested, clinical presentation and outcome of dogs with SE due to acute intoxication. The study was retrospective. Medical records of all dogs suffering from SE were reviewed (Jan 1, 2002 to April 30, 2009).

Results:
Fourteen dogs with SE due to acute intoxication were identified. Toxicological analyses (qualitative analysis with gas chromatography/mass spectrometry; n = 11) detected poisonings with carbofuran, criminidine, paraoxon, metaldehyde, strychnine and diazinon. In the other three cases the uptake of a known poison was observed (zink phosphate, metaldehyde). None of the dogs showed evidence of neurological disease up to the day of presentation. The dogs were hospitalised for 2–10 days (median 5 days). The survival rate was 85.7%. None of the dogs experienced any more seizures after discharge (median observation period 2.6 years).

Conclusion and clinical relevance:
Ancillary to the acute clinical presentation, preliminary reports (possible uptake of poisonous material) and an inconspicuous medical history may suggest a tentative diagnosis. Managed adequately, these patients can have a high survival rate. Clinicians should also keep uncommon intoxications in mind.


Schlüsselwörter
Vergiftung, Hund, Epilepsie, Fallserie, Organophosphat, Carbamate, Metaldehyde, Criminidine, Strychnin, Zinkphosphid

Zusammenfassung

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ment appropriate to the underlying disease condition. To date, relatively little is known about SE in dogs (48). Characterised by prolonged seizure activity, SE affects dogs of any sex, breed or age and may have numerous underlying causes (3, 31, 38).

The necessity to stop SE before the untreated seizure activity provoked neuronal damage has been repeatedly emphasised. This neuronal damage may occur after 20–30 minutes of untreated seizure activity (7, 24, 41). According to this timeframe, the updated definition of SE describes it as a continuous seizure activity that lasts for more than 5 minutes, or as two or more discrete seizures between which there is incomplete recovery of consciousness (9, 24, 25, 31, 39, 40).

During the course of untreated seizure activity, further complications like hypoxia, acidosis, cardiac arrhythmias, renal failure, rhabdomyolysis and disseminated intravascular coagulation may occur (24, 30). For this reason, SE is regarded as a medical emergency (24, 30).

The establishment of a specific therapy beyond seizure management requires knowledge of the underlying disease condition. Former studies have emphasised the importance of neuroimaging and cerebrospinal fluid analyses in dogs with SE because of the frequent occurrence of symptomatic epilepsy (31, 39). We recently determined that in our hospital up to 20% of dogs presenting with SE with no prior history of suffering from seizure disorder due to

### Table 1: Clinical signs and historical data on 14 dogs affected by poisoning and presenting with status epilepticus (SE).

<table>
<thead>
<tr>
<th>Case N°</th>
<th>Breed</th>
<th>Sex¹</th>
<th>Age (years)</th>
<th>Latency period until clinical signs appeared</th>
<th>Clinical signs at time of hospital admission</th>
<th>Poisoning</th>
<th>Location²</th>
<th>Toxicological analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Labrador Retriever</td>
<td>m</td>
<td>4.2</td>
<td>&lt; 30 min</td>
<td>Hypothermia (during anaesthesia hyperthermia), hypersalivation, SE</td>
<td>Crimidine</td>
<td>Field</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>Mixed breed</td>
<td>fs</td>
<td>3.3</td>
<td>Not observed</td>
<td>Tremor, miosis, SE</td>
<td>Zinc phosphide</td>
<td>Field (known pest control)</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>Mixed breed</td>
<td>f</td>
<td>13.1</td>
<td>&lt; 30 min</td>
<td>Hyperthermia, SE</td>
<td>Metaldehyde</td>
<td>Forest (ate dead bird)</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>Golden Retriever</td>
<td>fs</td>
<td>8.5</td>
<td>&lt; 30 min</td>
<td>Hyperthermia, SE</td>
<td>Metaldehyde</td>
<td>Garden (snail baits)</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>Beagle</td>
<td>m</td>
<td>3.6</td>
<td>Not observed</td>
<td>Hypothermia, miosis, SE</td>
<td>Metaldehyde</td>
<td>Garden (snail baits)</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>Bernese Mountain Dog</td>
<td>m</td>
<td>3.3</td>
<td>&lt; 30 min</td>
<td>Tremor, hyperthermia, hyperexcitability, SE</td>
<td>Strychnine</td>
<td>nd</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>Golden Retriever</td>
<td>fs</td>
<td>1.5</td>
<td>Not observed</td>
<td>Diarrhoea, hyperthermia, hypersalivation, SE</td>
<td>Carbofurane</td>
<td>nd</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>Newfoundland Dog</td>
<td>f</td>
<td>0.7</td>
<td>&lt; 30 min</td>
<td>Hyperthermia, SE</td>
<td>Metaldehyde</td>
<td>Garden (snail baits)</td>
<td>no</td>
</tr>
<tr>
<td>9</td>
<td>Mixed breed</td>
<td>fs</td>
<td>5.5</td>
<td>&lt; 30 min</td>
<td>Tremor, diarrhoea, vomiting, miosis, bradycardia, hypersalivation, SE</td>
<td>Paraoxone</td>
<td>nd</td>
<td>yes</td>
</tr>
<tr>
<td>10</td>
<td>Labrador Retriever</td>
<td>mn</td>
<td>4.6</td>
<td>Not observed</td>
<td>Hypersalivation, diarrhoea, SE</td>
<td>Carbofurane</td>
<td>Forest</td>
<td>yes</td>
</tr>
<tr>
<td>11</td>
<td>Leonberger</td>
<td>f</td>
<td>0.7</td>
<td>&lt; 30 min</td>
<td>Tremor, hyperthermia, SE</td>
<td>Crimidine</td>
<td>New house, old shed on the site</td>
<td>yes</td>
</tr>
<tr>
<td>12</td>
<td>Mixed breed</td>
<td>fs</td>
<td>3.4</td>
<td>&lt; 30 min</td>
<td>Tremor, hypersalivation, vomiting, diarrhoea, bradycardia, SE</td>
<td>Carbofurane</td>
<td>Walk in the field</td>
<td>yes</td>
</tr>
<tr>
<td>13</td>
<td>Golden Retriever</td>
<td>m</td>
<td>0.3</td>
<td>3 hours after walk</td>
<td>Miosis, SE</td>
<td>Diazinon</td>
<td>Forest</td>
<td>yes</td>
</tr>
<tr>
<td>14</td>
<td>Boxer</td>
<td>mn</td>
<td>8.2</td>
<td>&lt; 30 min</td>
<td>Tremor, hypersalvation, diarrhoea, SE, cardiac murmur</td>
<td>Carbofurane</td>
<td>Walk in the park</td>
<td>yes</td>
</tr>
</tbody>
</table>

¹ f = female, fs = spayed female, m = male, mn = neutered male
² Area of presumed uptake of poisonous material. nd = not determined
nd = not documented in medical records
Materials and methods

The medical records of dogs with SE admitted to the Clinic of Small Animal Medicine of Munich (Ludwig Maximilians University [LMU], Munich) between January 1, 2002 and April 30, 2009 were screened. The general inclusion criterion for this case series was initial presentation of SE caused by acute intoxication confirmed by an unequivocal history of intake of poisonous material (e.g., snail bait) or by the identification of a poison known to cause seizures through qualitative toxicological screening (thin-layer gas chromatography/mass spectrometry; Institute of Veterinary Pharmacology and Toxicology, LMU Munich) of stomach contents or body fluids. Furthermore, metabolic causes for SE were excluded by laboratory analysis at the time of admission in all dogs.

The data collected from the medical records included breed, sex, age at seizure onset, historical information (i.e., location of and, where available, the situation of the intake of poisonous material), the specific type of poison that caused the seizures, findings from clinical and neurological examinations, laboratory findings, diagnostic work-up, duration of hospitalisation and outcome.

The definition of SE used for case selection was a continuous seizure activity lasting at least 5 minutes, or two or more discrete seizures between which there was an incomplete recovery of consciousness (9, 24, 25, 31, 39, 40).

The final outcome for dogs discharged from the hospital was assessed by phone calls to the owners.

Results

Medical history

Fourteen cases of intoxication-related SE were identified. The historical data of these dogs presenting with SE due to acute poisoning are shown in Table 1. Of these 14 dogs, 6 were males (4 intact; 2 neutered) and 8 were females (3 intact; 5 spayed). With respect to the breed, mixed-breed dogs (n = 4) and Golden Retrievers (n = 3) were most frequently represented, followed by Labrador Retrievers (n = 2), one Beagle, one Boxer, one Leonberger and one Newfoundland. The body weight ranged from 7.4 to 48.0 kg, with a median of 25.0 kg. The age at onset of SE and therefore also the age at the time of acute poisoning ranged between 0.3 and 13.1 years (median 3.5 years).

The dogs admitted to the hospital were all from the Greater Munich area. Only three of the poisoned dogs (dogs Nos. 2, 3 and 11) lived in the city of Munich, but two of the owners (dogs Nos. 2 and 3) walked the dogs in rural areas at the city limit.

Most poisonings (n = 9) were noticed in the winter and spring months (December until April); two dogs took ill in June (Nos. 4 and 9), and three dogs in September (Nos. 8, 13 and 14).

The intake of suspicious material was observed by the owners of the seven dogs during a walk (Nos. 1, 2, 3, 10, 12, 13 and 14). One of these dogs (No. 2) ingested something “looking like poison” during a walk in the fields, and because she was worried about possible intoxication, the owner asked the farmer what he scattered on his field. In two cases (Nos. 4 and 8), the owners had scattered snail baits and observed their dogs ingesting it. In one case, the neighbours had scattered snail baits in the garden (No. 5). In this case, the owners did not observe the dog ingesting the toxin. The owners of one dog had moved recently to an old house where the dog had been freely roaming in the garden prior to the first signs of poisoning (No. 11). Site of intake of poisonous material of dogs 6, 7, and 9 was not documented in the medical records.

All the dogs had been neurologically inconspicuous up to the day of presentation and had never shown any evidence of a previous neurological disease related to SE. The dogs had no history of other diseases, except for one dog that had previously displayed evidence of heart disease.

Clinical presentation and management

The clinical signs are shown in Table 1, the management in Table 2 and the clinical pathology data in Table 3. On admission, each dog was routinely evaluated with a complete blood count, BUN, creatinine, and blood gas analyses including glucose,
sodium, potassium, and ionized calcium concentrations. A standard serum profile was obtained on the admission day or the next day when the dogs were admitted after hours. Table 3 shows only the parameters for which variances were observed.

Six dogs were pretreated by the referring veterinarian prior to presentation (Table 2). After admission to the hospital, SE was treated with rectal or intravenous diazepam or midazolam (Table 2). This was followed by intravenous phenobarbital (Luminal®) up to 20 mg/kg in nine cases and repeated propofol bolus to effect. All patients were anesthetized with either pentobarbital (Narcoren®, n = 12) or propofol (Narcofol®, n = 2) by continuous rate infusion. Anaesthesia was maintained with a continuous rate infusion (CRI) of pentobarbital at 1.6–4.8 mg/kg BW/h CRI.

Concurrently with the seizure management, decontamination was performed (Table 2). Four dogs (Nos. 2, 5, 9 and 12) were treated with repeated atropine injections (Atropinsulfat Braun®, 0.05–0.2 mg/kg BW every 6 hours) because of miosis (Nos. 3, 5 and 9) and/or bradycardia (Nos. 9 and 12).

### Table 2: Management and outcome of 14 dogs affected by poisoning and presenting with status epilepticus (SE).

<table>
<thead>
<tr>
<th>Case N°</th>
<th>Poison</th>
<th>Treatment prior to admission</th>
<th>In hospital treatment</th>
<th>Decontamination procedure</th>
<th>Duration of anaesthesia (h)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crimidine</td>
<td>Diazepam IM, xylazine IM, ½ loading dose phenobarbital</td>
<td>Diazepam1 IV, ½ loading dose phenobarbital (10 mg/kg), pentobarbital3,5</td>
<td>Gastric lavage, charcoal</td>
<td>120</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>Zinc phosphide</td>
<td>Diazepam IV, loading dose phenobarbital</td>
<td>Diazepam IV, atropine, furosemide, propofol4 (induction), pentobarbital3,5</td>
<td>Gastric lavage, charcoal</td>
<td>48</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>Paraoxone</td>
<td>–</td>
<td>Diazepam1 IV, phenobarbital2, pentobarbital3,5</td>
<td>–</td>
<td>48</td>
<td>Euthanised</td>
</tr>
<tr>
<td>4</td>
<td>Metaldehyde</td>
<td>–</td>
<td>Phenobarbital2, pentobarbital3,5</td>
<td>–</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>Metaldehyde</td>
<td>Diazepam IM, acepromazine IM</td>
<td>Diazepam1, atropine, phenobarbital2, pentobarbital3,5</td>
<td>–</td>
<td>48</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>Strychnine</td>
<td>–</td>
<td>Diazepam (rectal), phenobarbital2, pentobarbital3,5</td>
<td>Gastric lavage, charcoal</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>Carbofurane</td>
<td>–</td>
<td>Midazolam, phenobarbital2, pentobarbital3,5</td>
<td>Gastric lavage, colonic irrigation, charcoal</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>Metaldehyde</td>
<td>Xylazine IM</td>
<td>Diazepam1, propofol4 (induction), pentobarbital3,5</td>
<td>Gastric lavage, colonic irrigation, charcoal</td>
<td>72</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>Paraoxone</td>
<td>Diazepam IV, loading dose phenobarbital</td>
<td>Atropine, propofol4,5</td>
<td>Gastric lavage, colonic irrigation</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>Carbofurane</td>
<td>–</td>
<td>Pentobarbital3,5</td>
<td>Gastric lavage</td>
<td>48</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>Crimidine</td>
<td>–</td>
<td>Diazepam1, pentobarbital3,5</td>
<td>Colonic irrigation, charcoal</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>12</td>
<td>Carbofurane</td>
<td>Diazepam, apomorphine, atropine, adrenaline, propofol IV, isoflurane</td>
<td>Diazepam1, atropine, phenobarbital2, pentobarbital3,5</td>
<td>Gastric lavage, charcoal</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>Diazinon</td>
<td>–</td>
<td>Diazepam1, propofol4 (induction), pentobarbital CRI3,5</td>
<td>Gastric lavage, colonic irrigation</td>
<td>12</td>
<td>Survived</td>
</tr>
<tr>
<td>14</td>
<td>Carbofurane</td>
<td>–</td>
<td>Diazepam1 rectal/IV, phenobarbital2, propofol4 (induction), pentobarbital3,5</td>
<td>Gastric lavage, charcoal</td>
<td>12</td>
<td>Died</td>
</tr>
</tbody>
</table>

1 Diazepam was administered at 0.5–1 mg/kg BW IV, in some animals injections were repeated up to three times.

2 Phenobarbital: A loading dose of 20 mg/kg BW was administered IV to achieve phenobarbital serum concentration within the projected therapeutic range (15–45 μg/ml, volume of distribution in dogs 0.75 L/kg BW). This was given in fractionated doses (5 mg/kg BW every 15–20 minutes IV).

3 Pentobarbital: A bolus of 4 mg/kg BW was administered slowly IV until seizures ceased and for induction of anaesthesia in case of refractory status epilepticus. This was repeated up to three times until clinical seizures stopped completely. The animals were then intubated with endotracheal tubes and anaesthesia was maintained with a continuous rate infusion (CRI) of pentobarbital at 1.6–4.8 mg/kg BW/h CRI.

4 Propofol: Boluses of 1–4 mg/kg BW were repeatedly administered until clinical seizures stopped. Thereafter, patients were intubated and propofol was continued at 8–12 mg/kg BW/h CRI.

5 Anaesthesia was maintained with continuous rate infusion because of refractory status epilepticus.
Intravenous fluid therapy and maintenance therapy with phenobarbital (2.5 mg/kg BID) was initiated for all the dogs. Hypoglycaemia (No. 9 and 11) was treated with bolus of 25% dextrose and addition of 5% dextrose to the fluid regimen. Subsequently, blood glucose was monitored every 1–2 hours. In both dogs hypoglycaemia never reappeared and thus was attributed to prolonged seizure activity.

All the dogs were intubated with endotracheal tubes during anaesthesia and continuously monitored with an electrocardiogram and pulse oximeter. If the oxygen saturation fell below 90%, the dogs were turned over every hour and reintubated every 6 hours. The mucosa in the oral cavity was kept moist by humidification every 30 minutes, and the eyes were treated every 60 minutes with eye ointment (Vidisic®) to prevent corneal lesions. Except for one dog (No. 3) that developed aspiration pneumonia and another dog that had a cardiac arrest under anaesthesia on the day of admission (No. 14), no complications occurred during anaesthesia. The dog that died of a cardiac arrest (No. 14) showed signs of heart disease before SE.

The duration of the anaesthesia ranged from 12 to 120 hours, with a median of 24 hours. The exact time for each dog is shown in Table 2. The time of hospitalisation ranged from 2 to 10 days with a median of 5 days. None of the dogs underwent further diagnostic analyses, such as analysis of the cerebrospinal fluid, electroencephalographic (EEG) evaluation or MR imaging of the brain.

### Toxicological analyses

In 11 cases, serum, urine and stomach contents were submitted for toxicological analysis by gas chromatography/mass spectrometry (Institute of Veterinary Pharmacology and Toxicology, LMU Munich). The results of the toxicological analyses were available within 2 to 7 days (median 4 days). The poisons identified were carbofuran (n = 4), crimidine (n = 2), paraoxon (n = 2), metaldehyde (n = 1), strychnine (n = 1) and diazinon (n = 1).

In the other three cases, the intake of poisonous material was observed by the owners and the poisonous agent was well known by the owner. Suspicious material e.g. coloured granules were retrieved by the owners and the poisonous agent was well known by the owner. Suspicious material e.g. coloured granules were retrieved by the owners and the poisonous agent was well known by the owner.

### Outcome

The overall survival rate was 85.7% (12/14). One dog died from cardiac arrest under anaesthesia on the day of admission (No. 14). This dog had a history of heart failure prior to admission. Another dog (No. 3) was euthanised after 2 days in the hospital at the owner’s request due to prolonged SE, aspiration pneumonia and

### Table 3 Clinical pathology data from 14 dogs presenting with status epilepticus (SE) due to poisoning. Reference intervals: Haematocrit (HCT) = 35–58%; white blood cells (WBC) = 5.0–16.0 × 10⁶μl; alanine aminotransferase (ALT) = 16–91 U/l; total bilirubin = 0.0–4.8 μmol/l; total protein (TP) = 48.0–76.0 g/l; albumin (Alb) = 25.0–44.0 g/l; cholinesterase (CHE [butyl]) = 48.0–76.0 g/l; blood urea nitrogen (BUN) = 3.3–8.3 mmol/l; glucose (Gl) = 3.1–6.1 mmol/l; platelets (PLT) = 150–500 × 10⁶μl; prothrombin time (PT) = 13.8–23.2 sec; partial thromboplastin time (aPTT) = 10.0–13.1 sec; nd = not determined. Elevated values in bold letters.

<table>
<thead>
<tr>
<th>Dog No. (Toxin)</th>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
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<tr>
<td></td>
<td>Cri</td>
<td>Zin</td>
<td>Par</td>
<td>Met</td>
<td>Str</td>
<td>Car</td>
<td>Cri</td>
<td>Par</td>
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<td>WBC</td>
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<td>ALT</td>
<td>48</td>
<td>31</td>
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<td>3.0</td>
<td>3.1</td>
<td>5.5</td>
<td>1.8</td>
<td>0.6</td>
<td>2.8</td>
<td>3.2</td>
<td>2.7</td>
<td>3.4</td>
<td>5.2</td>
<td>0.7</td>
<td>3.65</td>
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Car = carbofuran, Cri = crimidine, Par = paraoxon, Met = metaldehyde, Str = strychnine, Dia = diazinon, Zin = zinc phosphate
suspicion of abdominal masses prior to the results from the toxicological report. No lesion was identified upon necropsy.

The other 12 dogs recovered from SE and were eventually discharged from the hospital. Neurologic examinations at the day of discharge were unremarkable in seven dogs; four dogs walked slightly ataxic and one dog (with crimidine intoxication) was tetraparetic when discharged. Antiepileptic therapy with phenobarbital (Luminal®) was gradually tapered over the 4 weeks after discharge in all dogs and then discontinued. All dogs discharged from the hospital (Nos. 1, 2, 4–13) were still alive and had recovered completely without any more seizures at the time of phone contact with the owners. Median follow-up time was 2.6 years (0.2–6.9 years).

### Discussion

In a recently published study from our service, one-fifth of dogs presenting SE as their first seizure suffered from acute poisoning. Consequently, advanced toxicological screening may be a useful supplementary tool in the diagnostic work-up of dogs with SE (48). In cases with a high suspicion of intoxication, magnetic resonance brain imaging could be postponed for a few days. This avoids the misinterpretation of transient changes in the T2-weighted images occurring after severe seizures (48). On the one hand, this avoids an additional required imaging, and on the other hand, this approach lowers the costs for the owners.

#### Age

The age distribution was wide, with a slight trend to younger dogs (median age 3.5 years). This may be due to the greater curiosity of younger dogs and a related disposition to ingest foreign bodies and, in the worst cases, poisonous material. On the other hand, old age did not protect against uptake of poisonous material, as demonstrated by a 13-year-old dog with organophosphate poisoning. One recently published review article about animal poisonings also reported that young dogs in particular, are most affected by poisonings (6).

#### Breed distribution

The breed distribution among the poisoned dogs indicates that mostly large breed dogs were affected. One possible explanation would be that large dogs are more likely to be kept or go on prolonged walks in rural areas where agricultural use of pesticides is possible.

#### Historical information

Most owners of poisoned dogs lived in the Greater Munich in rather rural areas, and two of the three owners who lived in the city walked the dogs in rural areas. These findings suggest that the risk of ingesting poisonous material seems to be much higher in these rural areas than in the city. Nevertheless, one dog (No. 14) acquired carbamylseleno following a walk in a park in downtown Munich (Nymphenburg). In six cases, the owners observed the intake of foreign material during a walk, and in the other six cases this was assumed because the neurological signs appeared shortly after a walk or after freely roaming in the garden.

The fact that many poisonings were noticed in the winter and spring months and only five cases occurred in summer is difficult to explain, although another study made similar observations (15). Sowing takes place in autumn and winter for the winter grain, as well as in spring for the spring grain. Therefore, anti-rat efforts (which endanger other animals as well) are practised more intensively in winter and spring than in summer (15).

#### Clinical signs

In most cases, a rapid onset of neurological symptoms like ataxia, tremors, muscle fasciculations associated with abnormal mental status, hyperventilation and progression to focal and generalised seizures, often associated with gastrointestinal symptoms, could be observed. This is characteristic of all ingested poisonous substances; they all have a short latency period until the onset of symptoms (13). Oral uptake of large amounts of organophosphates/carbamates can cause seizures within 10–20 minutes (44).

The clinical signs of all poisoned dogs involved the central nervous system and, in most dogs, the gastrointestinal system as well. SE was associated with hyperthermia ≥ 39.5 °C, hypersalivation, muscle tremors and diarrhoea in many dogs (Table 1). In dogs poisoned with organophosphates/carbamates, the typical indicator signs of organophosphate toxicity were not always evident; only two of the seven dogs showed miosis, and only one dog displayed bradycardia. However, five of these dogs showed hypersalivation. Miosis and hypersalivation may be common in SE due to other causes, and therefore, in individual cases presented to the emergency clinician, it may be difficult to decide whether hypersalivation represents a symptom of the cholinergic effect of organophosphates or if it is simply a symptom of ES and SE of any origin. Similarly, hyperthermia may be a consequence of SE of any cause due to excessive muscle activity. Therefore, besides the combination of tremors, seizures and gastrointestinal signs we were unable to identify any signs that appeared consistently and are typical for a specific intoxication.

All the detected toxic agents are potential convulsants. A remark must certainly be made concerning strychnine because the convulsions from this poison usually are at the spinal level due to an interaction with the inhibitory interneurons and glycineric neurotransmission, so the patient may be awake (42). However, local strychnine poisoning may cause epileptic seizures culminating in SE (43). The poisoned dog in our hospital was unconscious, and EEG conformation of epileptic seizures culminating in SE was not obtained.
Toxicological analyses

The detection of toxins with gas chromatography/mass spectrometry as done in this study is hampered by the fact that these methods demonstrate only exposure to toxins because of their qualitative but not quantitative nature. Yet, the combination of gas chromatography and mass spectrometry unifies the high sensitivity of gas chromatography and the high specificity of mass spectrometry, and thus enables structural determinations (18). Demonstration of exposure to a toxin in combination with the clinical signs permits a diagnosis of intoxication.

A broad spectrum of poisonous substances was identified. Among the identified categories were the insecticides (50.0%), or, more precisely, carbamates (carbofuran, n = 4) and organophosphates (paraoxone, n = 2; diazinone, n = 1), which are acetylcholinesterase inhibitors (14). The next-most common category were the rodenticides (28.6%), which are highly toxic to all mammals (crimidine, n = 2; zinc phosphide, n = 1; strychnine, n = 1). The third-most common group were the molluscicides (21.4%; metaldehyde, n = 3). A similar distribution (46.6% insecticides and 37.9% rodenticides) was reported in a study over 10 years ago from a veterinary analytical toxicology laboratory in Spain (19). In general, the insecticides and rodenticides are most frequently seen in poisonings of domestic animals and wildlife (5, 29). A significant problem is that pesticides are spread in rural regions without regard to their accessibility to companion pets and livestock. Also, secondary intoxication after the ingestion of dead birds may be possible.

Insecticides

Insecticides that were detected include organophosphates (paraoxone, diazinone) and carbamates (carbofuran). Poisonings with this group of toxins are not only appearing in animals, but they are also becoming an important global health problem (11, 15, 20). This group of poisonous substances represents the most frequently used insecticides worldwide. Their mode of action is inhibition of acetylcholinesterase at cholinergic synapses (both muscarinicergic and nicotinergic), which is reversible in the case of carbamates and irreversible in the case of organophosphates.

The carbamate carbofuran is highly toxic (acute oral $LD_{50} <$ 10 mg/kg BW) (20). In the last decade, the use of carbofuran has been severely restricted in Europe and North America because of the negative implications for non-target animals (46). A single granule may kill a small bird (45). In December 2008 an interdiction of carbofuran throughout the EU came into effect (EU directive 91/414/EWG). Dogs ingested carbofuran during a walk in a park in downtown, in a wood northwest of Munich (Sulzeemoos) and in a field (two dogs) in the same region (Marzling). One owner observed the dog eating a mouse. In this case we assume secondary poisoning after ingesting the poisoned cadaver.

Other poisonous substances from the insecticide group were the organophosphates paraoxone and diazinon, which were detected in three dogs. In Germany, diazinon is not permitted for use as a pesticide (Pflanzenschutz-Anwendungsverordnung [PflSchAnwV, 1992]). Nevertheless, a poisoned dog ingested this toxic agent during a walk in a forest. One dog with paraoxon poisoning ingested the cadaver of a bird. Presumably, also in this case secondary poisoning occurred.

The therapy for organophosphate and carbamate poisoning is aimed at the prevention of further absorption, which is achieved by the induction of emesis in asymptomatic patients and gastric lavage followed by charcoal administration (0.5–1 g/kg BW) and a cathartic in symptomatic anaesthetised and intubated dogs. Treatment with a muscarinic antagonist atropine in high dosages exceeding the usual preanaesthetic dose by factors of 4–10 (0.2–0.5 mg/kg BW IV or divided IV and SC; this may have to be repeated several times as indicated by the occurrence of salivation and bradycardia) is recommended (32). In this case series only two of the three dogs with insecticide poisoning required treatment with atropine because of miosis (No. 9) or bradycardia (Nos. 9 and 12).

The control of muscle tremors, agitation and seizures may require specific spasmolytic or anticonvulsant therapy with diazepam, methocarbamol (Robaxin®, 55–220 mg/kg BW every 6 hours IV), phe nobarbital or even low-dose propofol or continuous pentobarbital. Nicotinergic signs like muscle tremors and fasciculations can be specifically addressed with an oxime acetylcholinesterase reactivator such as obidoxime or pralidoxime (Toxogonin®, 2-PAM; 10–20 mg/kg IM or SC every 8–12 hours; needs to be given in the first 24 hours) or the antihistamine diphenhydramine (Betadorm®, 2–4 mg/kg BW every 8 hours) (32). However, the use of oxime reactivators is controversial in cases of carbamate poisoning because of its reversible mode of cholinesterase inhibition, and there is an ongoing discussion in human medicine about the necessity of their use and possible side-effects like tachycardia, muscle rigidity and transient laryngospasm if given rapidly intravenously (44). On the other hand, diphenhydramine (Betadorm®) may cause excessive sedation or excitation, so with either drug, the advantages need to be weighed against the disadvantages. None of the dogs in this case series received oxime reactivators or diphenhydramine.

Rodenticides

The second most commonly detected toxic agents in our study were the rodenticides.

Crimidine (2-chloro-4-dimethylamino-6-methylpyrimidine), known as Castrix®, is a fast-acting convulsant that is used to combat rodents (15, 23). It was developed during the Second World War and its convulsive effect has been known since that time (9, 22). Many years later its mode of action was investigated further, and crimidine was recognised as a vitamin B$_6$ antagonist. Vitamin B$_6$ is involved in the synthesis of gamma-aminobutyric acid (GABA), the most important inhibitory neurotransmitter (22). In the early 1980s, the first report of a dog poisoned with crimidine appeared (26). Previously, it had only been reported in indigenous carnivores (28).
One dog (No. 2) in this study suffered from zinc phosphide poisoning. This toxic agent is a highly effective rodenticide whose mechanism of toxicity is mediated by phosphine. Phosphine occurs if zinc phosphide contacts water or gastric acid (35). The clinical signs tend to occur rapidly after exposure and are characterised by lethargy, dyspnoea, ataxia, agitation, muscle tremors, seizures and occasionally haematemesis. Increasing the gastric pH is recommended to prevent further absorption (44). The acute poisoning of dog No. 2 was presumably due to the ingestion of the salt. Another mechanism of intoxication with zinc phosphide would be the inhalation of phosphine (35).

Strychnine has been used widely for years to kill predators. In the past, it was one of the major reported causes of dog poisonings (23). The use of strychnine as a pesticide is now restricted by law in many countries. Nevertheless, it is still occasionally used against birds, rodents or foxes (27). Therefore, the accidental poisoning of companion animals like dogs and cats is possible. Secondary poisoning after ingestion of a poisoned cadaver is also possible (13).

Molluscicides

Another group of toxic agents that consistently causes poisonings in dogs are the molluscicides. Three dogs in our study suffered from metaldehyde poisoning. Metaldehyde, used as snail or slug baits, is usually distributed as granules or pellets (46). In these pellets the active agent is blended with bran or corn, so it is very tasty for dogs (37). The mechanisms of action of metaldehyde are still unclear (37). In experimental studies metaldehyde was shown to enhance the activity of monoaminooxidase and diminish the activity of GABA, resulting in a decrease of the seizure threshold (37). There have been two retrospective case series on metaldehyde intoxication describing clinical signs like seizures, hyperthermia, tachycardia and muscle tremors (13, 44). In two cases of metaldehyde poisoning in our study, the dogs ingested snail bait that was distributed by the owners themselves (Nos. 4 and 8), and in one case (No. 5) by the neighbours in the garden. Clearly, there is an urgent necessity to educate owners about the risks of distributing snail baits in the garden (46).

Biochemical findings

The observed biochemical findings (Table 3) in this study were remarkable. The most common finding was an elevated haematocrit, presumably due to dehydration. The elevated levels of BUN often result from a transient prerenal azotaemia in patients with intoxication. Yet, elevated levels of BUN and creatinine could also indicate acute renal failure from rhabdomyolysis and myoglobinuria or the specific type of toxin (e.g. ethylene glycol, zinc phosphide) (36). An increased ALT activity may be due to hypoxia during SE. CK activity may be elevated due to excessive muscle activity during seizures. Two of the dogs showed hyperbilirubinaemia. One of these dogs suffered from metaldehyde poisoning, the second from crinidine poisoning. In metaldehyde poisonings, hepatic damage (hepatocyte degeneration) has been reported (9). The finding that five dogs showed increased glucose levels and two dogs decreased glucose levels may be explained by hyperglycaemia in the beginning of SE and the development of hypoglycaemia after long-lasting continuous seizures (> 60 minutes) (30). Also, in all dogs hypoglycaemia was treated and subsequent monitoring excluded severe recurrent hypoglycaemia. Yet, we cannot exclude the possibility that hypoglycaemia was a consequence of zinc phosphide or metaldehyde poisoning.

Surprisingly, only one dog with organophosphate intoxication and two dogs with carbamate poisoning showed a decline in butyryl cholinesterase activity. In two cases, the decrease in the activity was more than 50%, the level at which intoxication symptoms appear (34). Organophosphates and carbamates inhibit both enzymes, acetylcholinesterase (which can be found in the synaptic cleft and in erythrocytes, the brain and the retina) and butyrylcholinesterase (which is found in liver, pancreas, heart, white matter of the brain and serum) (30). One would expect a much more pronounced decrease in cholinesterase activity with organophosphate intoxication while on the other hand cholinesterase may reactivate rapidly and normal activities can occur with carbamate poisoning (46). Thus, there appears to be a high rate of false-negative results with the routine measurement of the butyrylcholinesterase activity similar to reports in the literature (44). Contributing factors to the variability of cholinesterase activity have been reported: Reactions between acetylcholinesterase and organophosphates can continue if blood samples are kept at room temperature (12). Whole-blood cholinesterase may be falsely reduced in anaemic dogs (44). Cholinesterase activity can recover with carbamate poisoning, incubation at ambient temperature and dehydration can contribute to increased levels (46).

Management

Treatment of the poisoned dogs was mainly symptomatic and supportive with seizure management, decontamination, intravenous fluid therapy and prevention of aspiration pneumonia. Only five dogs received specific antidote therapy. One dog was treated with vitamin B12 because of proven crinidine intoxication, and four dogs were initially treated with atropin because of suspected organophosphate/carbamate intoxication (Table 2). However, organophosphate/carbamate poisoning was only proven in two of four dogs treated with atropine, while the history strongly suggested zinc phosphide and metaldehyde intoxication in the two other dogs. On the one side, this demonstrates the low diagnostic yield of the clinical signs for a specific group of toxins. On the other side, one could debate whether the euthanised dog with paraxoxon poisoning (No. 14) would have recovered better with atropine therapy, and whether atropine should have been given to all dogs with suspected poisoning. In human patients with organophosphate poisoning atropine is commonly used as first-line therapy to control muscarinergic signs. Dosing is aimed to increase the heart rate above 80 beats per minute, systolic blood pressure above 80 mmHg.
and to rapidly reverse bronchospasm and bronchosecretion, and doubling doses every 5 minutes has been recommended (12). Atropine overdosage has been associated with agitation and hyperthermia in people (12). None of the dogs of this case series received any of the red blood cell cholinesterase reactivators (e.g. obidoxime, pralidoxime). In people, there is no evidence yet that the addition of cholinesterase reactivators to atropine improves survival.

Anaesthesia was necessary for all dogs because they were refractory to first-line antiepileptic therapy.

Most dogs (85.7%) admitted in SE because of poisoning recovered and were eventually discharged from the hospital. The fact that none of the dogs experienced any more seizures after discharge, provides additional support to the diagnosis of intoxication. This appears important, because the type of toxicological analysis used in this study served only as a sensitive qualitative analysis which can demonstrate the presence of a poison in the body, but not its concentration. Therefore, a positive toxicological analysis cannot exclude other causes of seizures unerringly. However, if the seizures were caused by something other than intoxication, they would have recurred. Fortunately few complications occurred besides mild aspiration pneumonia and problems with the catheter site.

Limitations of the case series

The main limitation of the study is the small number of patients and the various toxins found. A second limitation may be the bias regarding the patient selection. Also, the detected spectrum of poisonous substances may not reflect the situation in other areas or countries because the use of pesticides depends greatly on the type of agriculture and pest control in the region and their availability on the local market (16, 47).

Conclusions for practice

In our case series presented here, a multitude of poisons with excitatory action on the central and peripheral nervous system ultimately resulting in agitation, muscle tremors and SE were found. From these observations we concluded that poisoning is a common cause of status epilepticus in dogs in Germany, that the clinical signs of intoxicated dogs not always match the expected clinical signs even in dogs with organophosphate poisoning, that measurement of butyryl cholinesterase in serum can have variable results, and that poisoning can be confirmed by toxicological analysis of blood, urine or stomach contents. Specific treatment should therefore be directed against the clinical signs. If status epilepticus is managed adequately, these patients can have a high survival rate. This report should encourage practitioners to treat this life threatening medical emergency adequately and not to euthanise patients prematurely.

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References

R. Zimmermann et al.: Canine status epilepticus due to acute intoxication


Rezension

Blutegeltherapie


Gesa Schützenhofer, Giessen