Calcium channel blocker toxicity

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Abstract

Objective: Calcium channel blockers (CCB) are frequently prescribed for veterinary patients and the incidence of toxicosis secondary to these agents is increasing. The purpose of this review is to discuss toxicity of these agents and review therapeutic options.

Etiology: Calcium plays a vital role in maintaining cellular functions within the cardiovascular system. Toxicosis secondary to these drugs can have deleterious effects on vascular tone, cardiac contractility, as well as electrical conduction in the heart.

Diagnosis: The intitial diagnosis is often made based on history of ingestion, physical examination and electrocardiography. Definitive diagnosis of CCB overdose can be made via quantification of serum concentrations of the drug ingested.

Therapy: Initial therapy should consist of inducing emesis and administration of activated charcoal. Other potential therapies include intravenous calcium, parasympatholytics, sympathomimetics, glucagon, insulin and dextrose, placement of a temporary pacemaker, or calcium channel agonists.

Prognosis: There is little data on the outcome of CCB toxicosis. Aggressive management of these cases is necessary to try and minimize morbidity and mortality.

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Introduction

Although calcium channel blockers (CCB) are a common medication used in both veterinary and human medicine, there is little written on the toxicity that can be associated with these medications. Calcium channel blocking agents are frequently used in both veterinary and human medicine to treat heart disease, arrhythmias, hypertension, and more recently, acute renal failure. Toxicosis can occur due to ingestion or accidental administration of an owner's medication, animals ingesting a large amount of their own medication, or iatrogenic routes.

The incidence of CCB overdose is not known, but the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (NAPCC) consulted on more than 390 cases of CCB ingestion between the years 1995 and 2000.[1] This likely underestimates the actual number of cases, as not all CCB-induced toxicities are reported and some cases may not be recognized due to a general lack of knowledge about clinical signs associated with CCB toxicosis. Overdose can have life-threatening effects on heart rate, vasomotor tone and pulmonary function. It is therefore imperative that veterinarians are familiar with the clinical signs, diagnostic abnormalities, and therapeutic options associated with this condition.

Current published veterinary information

Although there is a large amount of data available on CCB toxicity in humans, there is a relative paucity of data on veterinary patients. An article on CCB toxicosis was published in 2000[1] which provided a brief overview of this syndrome. To date, there are only 2 published case reports in the veterinary literature regarding CCB intoxication.[2,3]

In a case report of a cat with verapamil toxicosis, the patient exhibited clinical signs of depression and recumbency within 30 minutes of the owner inadvertently administering an 80 mg tablet of verapamil (the owner's medication) to the cat.[2] The administered dose was 14.5 mg/kg, which is 2–5 times the recommended dosage. Physical examination and electrocardiography revealed bradycardia with atrioventricular (AV) dissociation and systemic hypotension (Doppler blood

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Table 1: Types of calcium channels and their respective stimuli

Type of calcium channel	Stimulus for activity
Receptor-operated channels	Binding of a specific ligand, such as a neurohormone, to receptors within the channel
Stretch-operated channels	Vascular stretch
Second messenger-operated channels	Intracellular second messengers, such as inositol phosphate
Voltage-sensitive calcium channels	Voltage change across the membrane, such as depolarization
Neuronal (N-type)	
Transient (T-type)	
Long lasting (L-type)*	*The only channels affected by calcium channel blocking agents

pressure of 48 mmHg).[2] Diagnosis was made based on the history of the owner mistakenly giving the cat their own verapamil. The cat was treated with gastric lavage, activated charcoal, atropine, calcium gluconate, and intravenous (IV) fluids. The patient survived to discharge after 48 hours of intensive care.

The most recent report outlines a case of an adult dog ingesting 95–109 mg/kg of the owner's sustained-release diltiazem.[3] The dog had clinical signs of intoxication including depression, hypotension, and cardiac arrhythmias. Treatment was attempted with multiple agents including atropine, calcium, dopamine, and glucagon. Although the glucagon was initially effective, the dog eventually became resistant and a temporary transvenous pacemaker was placed. The pacemaker was used for 19 hours, and the dog was discharged from the hospital 6 days after the intoxication.

The present review will provide additional details on the pathophysiology of the clinical signs associated with CCB intoxication and will outline various treatment options and the rationale for their use.

Etiology

In order to fully understand the effects of an overdose, it is necessary to understand the normal role that calcium plays in maintaining cellular functions as well as the mechanism of action of CCBs. Calcium plays a crit-

ical role in sinoatrial (SA) and AV nodal conduction and electrical depolarization and contraction of cardiomyocytes and vascular smooth muscle. Calcium channels include receptor-operated channels, stretch-operated channels, calcium channels operated by second messengers, and voltage-sensitive channels (Table 1). The receptor-operated channels include those that are stimulated by the binding of specific ligands, such as neurohormones, to a receptor within that channel. Vascular stretch leads to stimulation of stretch-operated channels. Calcium channels operated by second messengers open in response to intracellular second messengers such as inositol phosphate or adenosine 3':5'-cyclic phosphate. Voltage-sensitive channels open in response to voltage change across the membrane, such as that which occurs during depolarization.[4–6] CCB inhibit only voltage-sensitive channel activation and have little to no action on the stretch- or receptor-operated channels.

There are three basic types of voltage-sensitive channels, classified based on location, conductance, and sensitivity to voltage. These include neuronal (N-type), transient (T-type) and long lasting (L-type). L-type channels are found in numerous tissues, but the highest quantity are found in the atria, blood vessels, and skeletal muscle.[4] There are several different isoforms of the L-type channels located in various tissues including the heart, lung, and brain that may contribute to the variable actions of the different classes of calcium channel blocking agents.[4] The only channels that are responsive to the current CCBs are L-type calcium channels.[4,6]

The CCBs as a class have varied effects on vascular tone, cardiac contractility, and electrical conductance in the heart (Table 2). There are three classes of CCBs: phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and dihydropyridines (e.g., nifedipine, amlodipine). Each class affects vascular tone, cardiac contractility, and electrical conduction in the heart differently. Agents in the dihydropyridine class have marked effects on the vasculature, while having little to no effect on cardiac contractility and conductance. The phenylalkylamines and benzothiazepines have a more

Table 2: Common calcium channel blocking drugs and their respective cardiovascular effects

Compound	Family/class	Vasodilation	Suppression of cardiac contractility	Automaticity suppression (SA node)	Conduction suppression (AV node)
Diltiazem	Benzo	+++	++	+++++	++++
Verapamil	Phenyl	++++	++++	+++++	+++++
Nifedipine	Dihydro	+++++	+	+	0
Amlodipine	Dihydro	+++++	+	+	0

Benzo, benzothiazepines; Phenyl, phenylalkylamines; Dihydro, dihydropyridines. + relative effect on the cardiovascular system, 0 = no effect.

pronounced effect on nodal conduction and myocardial contractility.[1] The elimination half-life, as well as the peak plasma concentration, varies depending on the formulation.[1,4] These drugs are well absorbed orally, but the absorption can be delayed in sustained release formulations. Once absorbed, these agents undergo extensive hepatic metabolism and first pass clearance.[6] Reported elimination half-lives for CCBs in dogs and cats are between 2 and 30 hours.[1] The time to peak plasma concentration ranges from 20 to 45 minutes for the immediate-release forms, while the sustained-release forms have a peak plasma concentration at 4 to 12 hours.[1,4] The onset as well as duration of clinical signs in animals will vary greatly depending on both the formulation as well as the amount ingested. In the aforementioned case report, serum concentrations of diltiazem were undetectable approximately 48 hours post-exposure.[3] CCBs are extensively protein-bound, rendering techniques such as hemofiltration or hemodialysis ineffective at removing the toxin.[6]

Calcium is central to the conductance and contraction of the cardiomyocytes. Within the pacemaker cells of the SA and AV nodes, depolarization is dependent on the inward flow of calcium in order to initiate the action potential. CCB inhibit this inward flow, leading to decreased SA pacemaker activity and AV conductance.[4] This results in a decrease in the sinus rate or conductance of impulses through the AV node. Within the Purkinje cells and myocytes, the depolarization is dependant upon sodium, but the maintenance of the action potential is provided by the opening of the slow calcium channels (phase 2 of depolarization).

Within the myocytes themselves, depolarization leads to the opening of the membrane-bound L-type channels and influx of a small amount of calcium into the cytosol. The presence of this small amount of calcium in the cytosol is thought to trigger the release of a much larger quantity of calcium from the sarcoplasmic reticulum (Figure 1) into the cytosol. This is referred to as calcium-induced calcium release (CICR). Calcium that is released
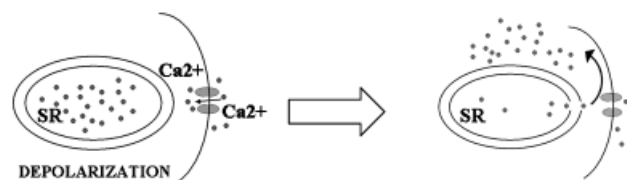

Figure 1: Calcium-induced calcium release within the myocyte. Depolarization of L-type calcium channels allows the influx of a small amount of extracellular calcium into the cell. This calcium then triggers the release of a larger amount of calcium from the sarcoplasmic reticulum (SR). This calcium then binds to troponin-C, allowing cross-linking of actin and myosin and resulting in contraction of the myocyte.

from the sarcoplasmic reticulum then binds to troponin C, which leads to a conformation change in the troponin-tropomyosin complex, exposing the actin filament and allowing cross-linking with myosin. Binding of actin and myosin leads to contraction of the myocyte.[4,6] CCB inhibit movement of calcium into the cell through the L-type calcium channels resulting in a decrease in the force of the myocardial contraction and inhibition of excitation-contraction coupling.[6]

In vascular tissue, the opening of the calcium channel leads to an increase in the cytosolic calcium concentration that results in the binding of calcium to calmodulin. This binding stimulates the phosphorylation of myosin that allows myosin to interact with actin, thereby causing smooth muscle contraction and vascular constriction.[4,6] CCBs, by inhibiting the rise in intracellular calcium concentrations, cause dilation of vascular tissue. The different calcium channel blocking agents have variable effects on vascular smooth muscle; it is believed that the extent to which the different vascular beds respond to these agents is related to their resting vascular tone.[4] In vascular beds where resting tone is normally high (e.g., coronary and skeletal muscle), CCBs have a more marked effect than in beds that have a lower resting tone (e.g., the gastrointestinal vasculature). Additionally, there is a dose-dependent response to CCBs within the systemic resistance vessels.[5] The venous capacitance vessels and pulmonary vasculature are much less sensitive to the vasodilatory effects of these drugs. These agents have very little effect on the vascular tone of the venous system at therapeutic concentrations.[5] In addition to the effects that CCBs have on the heart and vasculature, administration or overdose of CCBs can lead to hypoinsulinemia and hyperglycemia because the β cells of the pancreas also contain L-type calcium channels.[7]

More recently, the role of CCBs in the treatment of acute renal failure has been investigated. In renal transplant recipients, CCBs have been shown to minimize cyclosporin-induced hypertension and nephrotoxicity.[4,8,9] Currently, veterinary studies are underway to evaluate a protocol using diltiazem in cases of acute renal failure.[10] The mechanism behind the renal protective effects of CCBs is thought to be due to their ability to inhibit the cytosolic and mitochondrial accumulation of calcium. This accumulation of calcium can lead to the production of free radicals that can cause cell death. In addition, CCBs can inhibit the vasoconstriction mediated by endothelin, thereby improving renal blood flow.[4,10–12]

Clinical signs and diagnosis

Diagnosis is made based on history, physical examination, electrocardiography, and possibly quantification

of serum concentrations of the drug ingested. A complete history should be obtained to ascertain the dose, route, and formulation of the agent thought to be ingested or administered. In many cases, electrocardiography aids in the diagnosis of CCB toxicosis. Electrocardiographic changes can include a sinus bradycardia, AV dissociation, first-degree, second-degree or complete heart block, junctional escape rhythms, accelerated idioventricular rhythms, and asystole.[4]

Serum concentrations of the specific agent can be quantified utilizing high-performance liquid chromatography. Therapeutic concentrations of diltiazem in humans are reported as 0.05–0.2 p.p.m. (50–200 ng/mL); serious toxicity has been reported to occur at concentrations of 2.0 p.p.m. (2000 ng/mL).[a] In humans with acute myocardial infarction, the occurrence of second- and third-degree AV block and the need for a temporary pacemaker was substantially higher when drug concentrations exceeded 0.15 p.p.m. (150 ng/mL).[13] In a recent report of sustained-release diltiazem overdose in a dog, serious intoxication requiring transvenous pacing occurred at serum levels of 1.3 p.p.m. (1300 ng/mL) measured 18 hours after exposure.[3]

Previously reported clinical signs in animals and humans include hypotension, bradycardia, tachycardia, seizures, and pulmonary edema.[1–3,14,15] The mechanism behind the formation of edema has not been fully elucidated, but there are a number of proposed theories. It has been shown experimentally that CCBs may contribute to edema by either increased pulmonary capillary permeability or increased hydrostatic pressure.[14] These changes may occur due to the direct effect of calcium on cell shape, or via a mechanism that is mediated by the prostaglandins PGE_2 or PGF_2.[14] Another theory is that selective precapillary vasodilation from the CCBs, combined with excessive fluid therapy to treat the hypotension, leads to the formation of pulmonary edema.[16] Finally, it may be that massive sympathetic discharge secondary to the bradycardia and hypotension leads to the formation of neurogenic pulmonary edema.[14]

Therapy

General treatment and monitoring recommendations for intoxication: Owing to the severity of the clinical signs associated with an overdose, aggressive treatment and intensive monitoring is warranted in all patients that have ingested a potentially toxic dose. Inducing emesis is recommended if the patient is presented within 2 hours of ingestion and their neurologic and cardiovascular systems are unaffected. The emetic agent of choice in dogs is apomorphine. This drug causes emesis by stimulating the dopaminergic receptors in the chemoreceptor trigger zone, and may also

stimulate the emetic center itself.[17] The dose of apomorphine is 0.02–0.04 mg/kg. The tablets can be dissolved in sterile water and given through a filter IV or IM. Alternatively, the tablet can be placed in the conjunctival sac and rinsed out when sufficient vomiting has occurred.[17] In cats, xylazine can be used at a dose of 1.1 mg/kg IV or SQ. The emetic effects are mediated via effects on the α_2-adrenoreceptors or at opiate receptors. Xylazine can lead to sedation, respiratory depression and bradycardia. The reversal agents yohimbine or atipamazole may reverse these effects. The dose for yohimbine is 0.1 mg/kg IV and the dose for atipamazole is 0.2 mg/kg IV.[17,18] Hydrogen peroxide (3%), which can cause local gastric irritation, is another emetic commonly used in veterinary medicine. This can be used in both dogs and cats, and is useful as both a sole agent as well as in conjunction with the aforementioned drugs. The reported dose of hydrogen peroxide is variable, ranging from 1–2 mL/kg up to 5 mL/kg.[1,17] The reported maximum dose of hydrogen peroxide is 45 mL/patient.[1]

Although gastric decontamination is important in these cases, it is important to note that inducing vomiting in any bradycardic, hypotensive, or obtunded patient is contraindicated; gastric lavage with a protected airway is a safer option in these animals. Gastric lavage is also indicated in cases of massive ingestion. Care should be taken to both protect the patient's airway and to closely monitor the hemodynamic parameters. Finally, activated charcoal at a dose of 1 g/kg, with or without a cathartic, should be administered to adsorb any remaining toxicant and hasten elimination.

Fluid therapy should be instituted in order to maintain or improve hydration as well as to provide cardiovascular support. If the patient is hypotensive, aggressive fluid therapy with a balanced electrolyte solution is indicated. Care must be taken to not fluid overload these patients, as many will not have adequate cardiac output secondary to the negative chronotropic and inotropic effects of the CCBs. Placement of a central line in order to measure central venous pressure may assist the clinician in monitoring fluid therapy. Frequent assessment of the patient's respiratory status (i.e., monitoring respiratory rate, effort, and auscultation and performing pulse oximetry or arterial blood gas analysis) should be performed to monitor for hypoxemia, either due to fluid overload or noncardiogenic pulmonary edema. In any patient, close monitoring of heart rate, rhythm, and blood pressure is essential as dramatic changes can occur rapidly.

Specific therapies for CCB toxicosis: Although there is little data on the various treatment modalities for CCB toxicosis in veterinary patients, there are numer-

Table 3: Therapeutic strategies for calcium channel blocker toxicity

Therapy	Mechanism of action	Dosage
Calcium	Increases calcium available to the cells	Calcium gluconate 10%: 0.5–1.5 mL/kg IV slowly. Monitor heart rate and ECG while administering
Glucagon	Binding to specific receptors causing and increase in intracellular cAMP	Experimental study in dogs: 0.2–0.25 mg/kg bolus followed by a CRI of 150 μg/kg/min
Insulin and dextrose	Postulated that this therapy improves carbohydrate uptake in myocytes and smooth muscle cells	Experimental study in dogs: insulin infusion of 4 U/min with dextrose 20% solution to maintain normal blood glucose levels. Requires central venous catheterization and concurrent potassium supplementation to avoid hypokalemia
Temporary cardiac pacemaker	Improves heart rate and cardiac output	
Calcium channel agonists	Dihydropyridine compound that acts as a direct calcium channel agonist	Not available commercially, only utilized in research setting

c-AMP, cyclic-adenosine monophosphate; CRI, continuous rate infusion; IV, intravenous.

ous papers in the human literature describing different therapies.[16,19,20–33] Despite these data, the optimal treatment has yet to be determined. The following discussion will address the different treatment options, as well as the physiologic basis for each of the therapies (Table 3).

Calcium: The initial treatment for CCB toxicosis commonly consists of IV calcium. This treatment is readily available and is easily administered via a peripheral or central catheter. The administration of IV calcium causes an increase in the extracellular calcium concentration as well as in the free (unbound) calcium available to the cells; it may also increase the release of calcium from the sarcoplasmic reticulum.[6] Calcium gluconate 10% can be given at a dose of 0.5–1.5 mL/kg IV slowly while monitoring the ECG closely.[1] The optimum dose for calcium gluconate has yet to be determined, but calcium levels should be measured to monitor for hypercalcemia. There is a report in the human literature of a massive nifedipine overdose treated successfully with a continuous rate infusion (CRI) of calcium chloride (CaCl).[16] The authors' opinion was that calcium chloride was superior to calcium gluconate, as the concentration of calcium ion is higher (13.6 mEq *versus* 4.5 mEq in 10 mL of a 10% solution). The patient remained on the calcium chloride CRI for 60 hours with no major adverse reactions. The patient did, however, develop necrosis over the IV site secondary to extravasation of the CaCl. Although treatment with IV calcium is successful in some cases, the clinical efficacy of this treatment is not consistent and there is no documented dosage for therapy.[16] Owing to these facts, additional therapies are required in many patients.

Parasympatholytics and sympathomimetics: Atropine is a vagolytic that is frequently given in an attempt to treat the bradycardia associated with CCB toxicosis.

There is little data regarding the effectiveness of atropine for the treatment of CCB-induced bradycardia in veterinary medicine, but in human medicine it is thought to be of little value.[6,19]

There are numerous case reports of humans treated with various catecholamines and sympathomimetic agents, all with variable results. Agents utilized have included isoproterenol, dopamine, dobutamine, epinephrine, and norepinephrine, either alone or in combination with other drugs.[6,19–22] No single agent or combination of agents has been shown to be consistently effective.

Glucagon: Glucagon is a polypeptide hormone that has been shown to improve or reverse the bradycardia and hypotension induced by CCBs, both clinically and experimentally.[23–28] The exact mechanism of action of glucagon is not clear, but it appears that glucagon binds to specific cardiac receptors that are unaffected by CCBs.[6,24] This binding leads to an increase in the intracellular cyclic-adenosine monophosphate (cAMP) concentrations. This increase in cAMP results in an increase in the transcellular flux of calcium, which ultimately causes an increased intracellular myocyte calcium concentration. This increase in calcium concentration within the myocyte results in increased cardiac contractility and impulse generation.[6,25,26] The reported dose of glucagon in humans is variable. Treatment for experimental verapamil overdose in dogs used a 2.5 mg (approximately 0.13 mg/kg) glucagon IV bolus followed by an infusion at 2.5 mg/hr (approximately 0.13 mg/kg/hr) and resulted in improvement of the bradycardia and cardiac output, while having little to no effect on the hypotension.[24] In another experimental study evaluating the use of glucagon in the treatment of verapamil toxicity, treatment with glucagon (0.2–0.25 mg/kg bolus infusion followed by 150 μg/kg/min infusion) resulted in a transient resto-

ration of sinus rhythm, but all dogs in which it was effective reverted back into AV dissociation.[28] In a case report of intoxication in a dog, bolus dosages of 0.022–0.044 mg/kg and infusion doses of 0.036–0.040 mg/kg/hr were utilized. This dog responded initially, but did eventually require additional therapeutic intervention.[3] Administration of glucagon can be expensive; the cost of glucagon at our institution is $125.00 per 1 mg vial.

Insulin and dextrose: Hypoinsulinemia and hyperglycemia is a common consequence of CCB toxicosis, due to the inhibitory effect of these agents on insulin release from the pancreatic β cells.[1] Recent experimental studies in dogs[28] and clinical reports in humans[7,29,30] indicate that hyperinsulinemia-euglycemia therapy may be an effective alternate treatment. With this therapy, insulin is administered in combination with a dextrose solution to maintain normal blood glucose levels. In a normal patient, myocytes oxidize free fatty acids to provide their metabolic energy. In a stressed state or in cases of blockage of L-type calcium channels, it is thought that myocytes become more dependent on glucose for fuel. This dependence upon glucose for energy, combined with hypoinsulinemia, results in prevention of glucose uptake into the myocardial cells and decreased myocardial carbohydrate metabolism.[7,31] Hyperinsulinemia-euglycemia therapy results in an improvement in inotropy and systemic vascular resistance and reverses acidosis.[7] It is postulated that this improvement is due to improved carbohydrate uptake by myocytes and smooth muscle cells.

In experimental studies of verapamil intoxication in anesthetized dogs, an insulin infusion of 4 U/min with a 20% dextrose solution to maintain euglycemia, as well as potassium supplementation, was superior to calcium, epinephrine, and glucagon at improving survival and maintaining myocardial contractility.[28,31] There are similar reports of successful treatment utilizing hyperinsulinemia-euglycemia therapy in human patients.[7,29] Insulin and dextrose are commonly available to veterinarians, and this may provide a readily available alternate therapy for cases in which calcium or vasopressor support fails. It should be noted, however, that the administration of 20% dextrose should be given through a central catheter to avoid phlebitis, and frequent monitoring of the patients blood glucose levels is necessary to avoid severe hypo- or hyperglycemia.

Other therapeutic options: In cases of severe bradycardic conduction disturbances unresponsive to medical therapy, a temporary cardiac pacemaker may be necessary to improve the heart rate and cardiac output. The pacing will improve the heart rate, and therefore will improve cardiac output, because cardiac output is the product of heart rate and stroke volume. However, this therapy may not correct all of the other effects of CCB overdose, such as negative inotropy and vasodilation.

Experimentally, calcium channel agonists have been utilized to counter the effects of CCB overdose. These agonists, including 4-aminopyridine and Bay K 8644, have both have been shown to reverse the toxicity of verapamil in experimental animals.[32] In addition, 4-aminopyridine has been used in conjunction with hemodialysis in a case of verapamil intoxication in a human with subsequent improvement in both blood pressure and cardiac conduction.[33] Although these agonists show promise, they are currently only available in the research setting.

Prognosis

Owing to the paucity of reports of CCB overdose in veterinary medicine, there is little data on the prognosis for patients presented with clinical signs of toxicity. Owing to the severity of the clinical signs that can be associated with CCB toxicosis, aggressive treatment is warranted. It is important to note that with intensive management, a favorable outcome can be achieved in some veterinary patients.

Recommendations for future studies

Based on both experimental and clinical data, there is no single treatment that is consistently effective in the treatment of CCB overdose. Based on this information, veterinarians should consider other treatment modalities for those cases that do not respond to calcium alone. Owners should be warned about the potential toxicities associated with these agents when prescribing them for the management of cardiac disease or hypertension. Further studies to evaluate treatment response and outcome in veterinary cases should be performed.

Footnote

[a] Product monograph, Cardizem CD, Biovail Laboratories Incorporated, Morrisville, NC, 2002.

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