Unusual case of pleural effusion caused by amlodipine in a dog with systemic hypertension

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Abstract

Objective: The aim of this report is to document the case of a dog that developed pleural effusion as a potential side-effect to the administration of a high-dose of amlodipine.

Case summary: A Yorkshire terrier dog (13-year-old, castrated male, 4.5 kg) presented with severe systemic hypertension (>200 mmHg), hyperkalaemia, and acute pancreatitis. The dog had hyperadrenocorticism, chronic valvular heart disease, chronic kidney disease, and cerebellar infarction as underlying diseases. Additionally, the dog had laboured breathing and tachypnoea during hospitalization. Screening examinations revealed a pleural effusion (pure transudate) for which hypoalbuminemia and thromboembolism were ruled out as the causes. Therefore, the adverse drug event of an antihypertensive drug (amlodipine) was tentatively diagnosed.

Conclusions: Pleural effusion resolved within 24 h of reducing the dosage of amlodipine. Hence, the dog was diagnosed with amlodipine-induced pleural effusion. Rarely, amlodipine can cause pleural effusion after high-dose administrations in humans, but only two cases of peripheral edema have been reported in animals. If pleural effusion occurs in hypertensive patients administered amlodipine, it should be considered as the potential cause.

Keywords

adverse drug event, amlodipine, dog, pleural effusion, systemic hypertension

1 | INTRODUCTION

Pleural effusion can cause dyspnoea in dogs, and primary causes are diagnosed according to the type of pleural effusion. For example, protein-poor effusions with low cellularity and pure transudates can occur secondarily to hypoalbuminemia, increased intravascular hydrostatic pressure, portal hypertension, cirrhosis, lymphatic obstruction, and congestive heart failure (Dempsey & Ewing, 2011). The effective treatment of pleural effusion depends on accurately identifying the underlying cause.

In human studies, pleural effusion may occur as an adverse drug event of amlodipine, but the mechanism is unclear (Chaouat et al., 1996; Karaca et al., 2016). Amlodipine is a calcium channel blocker (CCB) that is commonly used to treat systemic hypertension in human and veterinary patients. By blocking voltage-sensitive calcium channels (L-type), calcium entry into vascular smooth muscle cells and myocytes is reduced, leading to vasodilation (Cooke & Snyder, 1998). Pleural fluid associated with CCB in humans is a rare adverse drug event that occurs when CCB is administered at a high dose (Chaouat et al., 1996). Although the exact mechanism is unknown, CCB selectively dilates the...
precapillary vessel, causing increased blood flow and hydrostatic pressure, leading to fluid accumulation (Pedrinelli et al., 2001). CCB also accumulates fluid by interfering with myogenic response (Pedrinelli et al., 2001). These adverse drug events are rarely reported in human medicine and only two cases of peripheral edema have previously been reported in veterinary medicine (Creevy et al., 2013; Plumb, 2018; Ramsey, 2011). Here, we describe a case of pleural effusion thought to be secondary to the administration of a high-dose of amlodipine in a dog.

## 2 | CASE PRESENTATION

A 13-year-old spayed male Yorkshire terrier weighing 4.5 kg was admitted to the hospital for hyperkalaemia, aggravated azotaemia, and acute pancreatitis. The dog had been managed with severe hypertension (>200 mmHg), proteinuria, hyperadrenocorticism, myxomatous mitral valve degeneration ACVIM stage B1 with a heart murmur (grade 4/6), chronic kidney disease (CKD) IRIS stage 2, and cerebellar infarction as underlying diseases. Cerebellar infarction had been diagnosed using magnetic resonance imaging 6 month prior.

On days 0–4, vital signs were stable, and there were no signs of respiratory problems. Body weight was 4.46 kg on day 0 and increased to 4.94 kg on day 4. Hyperkalaemia and azotaemia were corrected with fluid therapy of 0.45% N/S with 2.5% dextrose and multiple injections of regular insulin 0.1 IU/kg subcutaneous and 20% glucose 15 ml intravenous (IV). The blood analysis showed that blood urea nitrogen (BUN) was decreased from 57 to 49.9 mg/dl (reference range 9.6–31.4 mg/dl), creatinine was decreased from 3.1 to 1.34 mg/dl (reference range 0.4–1.3 mg/dl), and inorganic phosphate was decreased from 12.6 to 8.5 mg/dl (reference range 2.3–6.3 mg/dl). Potassium was corrected from 9.1 to 4.2 mmol/L (reference range 3.6–5.5 mmol/L). The symptoms of pancreatitis improved during hospitalization with the following treatment: maropitant 1 mg/kg IV q24h, omeprazole 1 mg/kg per oral (PO) q12h, hydromorphone 0.1 mg/kg injections, and gabapentin 10 mg/kg PO q12h. However, despite nitroprusside 3–4 µg/kg/min IV continuous rate infusion, multiple injections of hydralazine 0.5–1 mg/kg IV, phenoxybenzamine 1.5 mg/kg of q12h PO, amlodipine 0.4 mg/kg q12h, and analgesic treatment, systolic blood pressure did not decrease below 180 mmHg.

On day 5, the dog displayed laboured breathing and tachypnoea, and hypertension was still not corrected. Body weight was 4.98 kg, and the blood analysis showed that BUN was 52.1 mg/dl, creatinine was 1.3 mg/dl, and potassium was 3.54 mmol/L. Thoracic radiography revealed pleural effusion as a widened interlobar fissure and scalloped sign (Figure 1a). Systemic screening tests, including physical examination, blood analysis, urine analysis, echocardiogram, and cytological examination of the pleural fluid, were performed to determine the cause of the tachypnoea. In physical examination, systolic blood pressure was measured as 200 mmHg by the Doppler method. Azotaemia (blood urea nitrogen 52.1 mg/dl; reference range 9.6–31.4 mg/dl), mild hypoalbuminemia (2.46 g/dl; reference range 2.6–4.4 g/dl), and increased canine pancreas-specific lipase were detected in the laboratory results (over 2000 ng/ml; reference range 0–200 ng/ml, Table 1). The echocardiography revealed no remarkable findings indicating heart failure or pulmonary hypertension. Then, 140 ml of pleural effusion was removed through thoracocentesis. Cytological examination of the pleural fluid revealed a transudate with a total protein < 2.0 g/dl and a nucleated cell count of 150 cells/µl. There were no remarkable cells except for a small number of neutrophils and lymphocytes.

Since the patient had severe hypertension with proteinuria, we suspected that hypoalbuminemia or overhydration was the cause of the pleural effusion. The other cause of pleural effusion was considered to be the increased hydrostatic pressure caused by anti-hypertensive drugs such as hydralazine and amlodipine. Other differentials for the pleural effusion, including right-sided heart failure, thromboembolism, tumour, inflammation, herniation, or as a secondary symptom to chronic pancreatitis, were ruled out through blood analysis and diagnostic imaging.

**FIGURE 1** Thoracic radiographs of the patient with pleural effusion. (a) Day 5: bilateral pleural fissure lines were present on the ventrodorsal projection and there was retraction of the ventral lung margin, creating a scalloped appearance on the lateral view consistent with pleural effusion. Vertebral heart score was 10.7 vertebrae and there was straightening on the caudodorsal portion of the cardiac silhouette consistent with left atrial enlargement. (b) Day 8: persistent of pleural effusion was found after 2 days of decreasing fluid input and removing pleural fluid by thoracocentesis. (c) Day 16: There was no evidence of pleural effusion 5 days after reducing the dose of amlodipine.
First approach to differential diagnosis of pleural effusion was ruled out overhydration. During hospitalization, the urine volume was 1.2–2.09 ml/kg/h despite there being 2.5 ml/kg/h fluid input. Considering the insufficient urine output, overhydration was ruled in. Overhydration could be caused by fluid input, but also a secondary response to reductions in glomerular filtration rate. However, the kidney panel was improved as the BUN was 52.1 mg/dl and the creatinine was 1.30 mg/dl after fluid therapy and the urine-specific gravity was 1.010. Considering the blood and urine analyses, to further investigate the effect of fluid administration on pleural effusion, we reduced the fluid input from 2.5 ml/kg/h to 1.25 ml/kg/h. After decreasing the fluid input rate until day 8, fluid input and urine output were matched, but pleural effusion was still identified. Moreover, the patient did not have any other clinical signs of overhydration, so overhydration was ruled out as the cause of the pleural effusion. Additionally, even after the albumin level was corrected within the normal range without special treatment, pleural effusion was persisted (Figure 1b).

On day 8, we decided to reduce the dose of anti-hypertensive drugs. Hydralazine and nitroprusside injection for systemic hypertension were stopped, but pleural effusion was found again on day 11. Then, the dose of amlodipine was reduced from 0.4 mg/kg PO q12h to 0.3 mg/kg PO q12h. Twenty-four hours after reducing the dose of amlodipine, laboured breathing was not observed.

On day 16, pleural effusion was not identified on thoracic radiography. To rule out overhydration, the administration rate of the fluid was reduced, but the pleural effusion remained. While the body weight was serially measured, no correlation between fluid rate and pleural effusion was consistently detected. Tumour, inflammation, and thromboembolism, or overhydration. This patient had mild hypoalbuminemia and chronic pancreatitis. Even after hypoalbuminemia and inflammation were corrected, the pleural effusion was consistently detected. Tumour, inflammation, thromboembolism, herniation, right-sided heart failure, and pulmonary hypertension were not found on the echocardiography or thoracic radiography. To rule out overhydration, the administration rate of the fluid was reduced, but the pleural effusion remained. While the body weight was serially measured, no correlation between fluid rate and pleural effusion was found (Figure 2).

| Day | Reference range | Albumin 2.6–4.4 g/dl | BUN 9.6–31.4 mg/dl | Cr 0.4–1.3 mg/dl | Phosphate 2.3–6.3 mg/dl | Na+ 145.1–152.6 mmol/L | K+ 3.6–5.5 mmol/L | cPL 0–200 mg/ml | CRP 0–20 mg/L | UPC 0.0–0.5 |
|-----|----------------|----------------------|-------------------|-----------------|------------------------|------------------------|-----------------|----------------|----------------|------------|
| 0   | >200           | 2.6±1.5              | 57±2               | 3.1±0.9         | 12.6±8.9               | 148±144.6              | 9.1±5.85        | 0±400         | 0±100         | 0.5±0.2   |
| 3   | 200±195        | 2.4±1.6              | 51.6±8             | 1.58±11.6       | 8.9±5.1                | 151.8±152             | 3.9±200         | >2000          | 98.3±52.8     | 8±5.2     |
| 5   | 195±190        | 2.67±1.7             | 52.1±7             | 1.16±1.2        | 5.1±8.9                | 152±151.8             | 3.9±200         | >2000          | 25.8±12.4     | 8±5.2     |
| 8   | 190±180        | 2.79±1.8             | 60.3±6             | 1.26±1.6        | 5.8±8.8                | 147.9±148.9           | 3.9±200         | >2000          | 12.4±10       | 8±5.2     |
| 11  | 150±147        | 2.46±1.9             | 52.5±5             | 2.02±2.0        | 8±5.2                  | 148.9±144.8           | 3.9±200         | >2000          | <10±10        | 8±5.2     |
| 16  |                |                      | 51.4±4             | 0–200           | 3.4±2.4                |                        |                 |                |               |           |
| 23  |                |                      |                    |                 |                        |                        |                 |                |               |           |

Abbreviations: BUN, blood urea nitrogen; cPL, canine pancreas-specific lipase; Cr, creatinine; CRP, C-reactive protein; SBP, non-invasive systemic blood pressure; UPC, urine protein creatinine ratio.

### Discussion

To the best of our knowledge, this is the first report of suspected amlodipine-induced pleural effusion in a dog. Amlodipine is an antihypertensive drug and CCB, which blocks calcium ion influx into the vascular smooth muscle cell membrane and dilates peripheral arterioles (Stepien et al., 2002). Peripheral edema is a common adverse drug event of CCB therapy in human medicine, but pulmonary edema or pleural effusion has rarely been reported (Chaouat et al., 1996). In human medicine, there are a few reports of CCBs such as amlodipine, verapamil, and diltiazem causing pleural effusion (Chaouat et al., 1996; Erdogan et al., 2017; Hedaiaty et al., 2015; Karaca et al., 2016; Kim et al., 2015; Raptis et al., 2007), most of which were transudate.

The mechanism of CCB-induced pleural effusion is not completely understood. In humans, CCB-associated pleural effusion appears to be associated with eosinophilic pleural effusion, secondary to an immunemediated reaction (Raptis et al., 2007). However, in this case, remarkable cells were not found during the cytological examination. Vasodilatory edema is one of the common adverse events of anti-hypertensive therapy (Messerli, 2001) caused by increased intracapillary pressure. Thus, the adverse drug event of amlodipine in the pleural effusion might be associated with intracapillary pressure. CCB acts on the arteriole vessels and dilates the arterioles, while its vasodilatory effects on the veins are relatively lower. Thus, it is assumed that when high doses of amlodipine are administered, blood flow into the capillary bed increases as the arterioles dilate, but the veins are relatively undilated. Consequently, the hydrostatic pressure between the capillary bed and vein is increased, which leads to edema (Pierce et al., 2011). In this patient, there were no evidence of other causes for the transudate pleural effusion, such as right-sided heart failure, hypoalbuminemia, tumour, inflammation, herniation, thromboembolism, or overhydration. This patient had mild hypoalbuminemia and chronic pancreatitis. Even after hypoalbuminemia and inflammation were corrected, the pleural effusion was consistently detected. Tumour, inflammation, thromboembolism, herniation, right-sided heart failure, and pulmonary hypertension were not found on the echocardiography or thoracic radiography. To rule out overhydration, the administration rate of the fluid was reduced, but the pleural effusion remained. While the body weight was serially measured, no correlation between fluid rate and pleural effusion was found (Figure 2).

### Table 1 Monitoring of systemic blood pressure and laboratory results of patient during hospitalization

| Day | Reference range | SBP 110–160 mmHg | Albumin 2.6–4.4 g/dl | BUN 9.6–31.4 mg/dl | Cr 0.4–1.3 mg/dl | Phosphate 2.3–6.3 mg/dl | Na+ 145.1–152.6 mmol/L | K+ 3.6–5.5 mmol/L | cPL 0–200 mg/ml | CRP 0–20 mg/L | UPC 0–0.5 |
|-----|----------------|-----------------|---------------------|-------------------|-----------------|-------------------------|------------------------|-----------------|----------------|----------------|------------|
| 0   | >200           | 200±195        | 2.6±1.5             | 57±2              | 3.1±0.9        | 12.6±8.9                | 148±144.6              | 9.1±5.85         | 0±400         | 0±100         | 0.5±0.2   |
| 3   | 200±195        | 2.46±1.7       | 51.6±8              | 1.58±11.6         | 8.9±5.1        | 151.8±152              | 3.9±200                | 3.9±200         | >2000         | 98.3±52.8     | 8±5.2     |
| 5   | 195±190        | 2.67±1.8       | 52.1±7              | 1.16±1.2          | 5.1±8.9        | 152±151.8              | 3.9±200                | 3.9±200         | >2000         | 25.8±12.4     | 8±5.2     |
| 8   | 190±180        | 2.79±1.9       | 60.3±6              | 1.26±1.6          | 5.8±8.8        | 147.9±148.9            | 3.9±200                | 3.9±200         | >2000         | 12.4±10       | 8±5.2     |
| 11  | 150±147        | 2.46±1.9       | 52.5±5              | 2.02±2.0          | 8±5.2         | 148.9±144.8            | 3.9±200                | 3.9±200         | >2000         | <10±10        | 8±5.2     |
| 16  |                |                | 51.4±4              | 0–200             | 3.4±2.4        |                        |                        |                 |                |               |           |
| 23  |                |                |                    |                   |                |                        |                        |                 |                |               |           |
body weight was found (Figure 3a). The sodium concentration was almost stable between 145–150 mmol/L (Figure 3b). The packed cell volume was not significantly decreased (Figure 3c); thus, there was no sufficient evidence for overhydration.

The patient had many comorbidities and was receiving treatments such as trilostane, phenoxybenzamine, anti-coagulants, and antibiotics. The mechanisms may be multi-factorial and may have been influenced by the underlying diseases and other drugs that enhance the vasodilatory effect of amlodipine or increase the hydrostatic pressure (Gupta & Kerai, 2018). However, considering that the pleural effusion had rapidly improved after reducing the amlodipine, we suspect that this was a case of amlodipine-induced pleural effusion.

In humans, CCB-induced pleural effusion occurs at high or toxic doses (Kim et al., 2015). The reference dosage of amlodipine in dogs is 0.1–0.5 mg/kg every 12–24 h (maximum dose 1 mg/kg/day) (Plumb, 2018). Although we administered the maximum dose of amlodipine that was within the reference range, pleural effusion occurred in this patient. Although this patient had CKD as an underlying disease, 90% of the amlodipine is metabolized in the liver and eliminated through faeces and urine (Stopher et al., 1988); therefore, the possibility of over-accumulation of amlodipine is unlikely. In a previous veterinary study, there were two cases of peripheral edema as an adverse drug event of amlodipine in which they were administered the maximum dose of amlodipine (Creevy et al., 2013). However, in this case, pleural effusion could have occurred within the reference dosage range and might not be related to overdose toxification. In previous human cases, CCB-induced pleural effusion was improved by stopping the medication, and hence it was diagnosed as an adverse drug event of CCB (Kim et al., 2015, Yılmaz et al., 2016). However, pleural effusion or edema caused due to overdosing of amlodipine is rarely improved even when medication is stopped and can be life-threatening. Several studies have reported hyperinsulinemic-euglycemic therapy as a first-step treatment for CCB overdose (Kline et al., 1995).

Another interesting point in this case was the severe systemic hypertension. In this patient, hyperadrenocorticism is suspected to be the leading cause of hypertension, but underlying diseases such as CKD and pheochromocytoma could also affect hypertension. However, even with various anti-hypertensive drugs including phenoxybenzamine, enalapril, and amlodipine were administered, but none were successful. After trilostane administration, blood pressure was decreased under 160 mmHg. However, severe hyperkalaemia occurred even when the dosage of trilostane was not as high as 1 mg/kg PO q12h. We assumed that trilostane could suppress mineralocorticoids in adrenal gland (Feldman, 2011; Lemetayer & Blois, 2018) and administered trilostane with a desoxycorticosterone injection. On day 16 after administration of the mixture, systemic hypertension was corrected, and hyperkalaemia did not occur even with the same dosage of trilostane and reduced dosage of other anti-hypertensive drugs.

4 Conclusion

This is the first report of suspected high dose amlodipine-induced pleural effusion in a dog. As the dosage of amlodipine was reduced, the
pleural effusion improved and was effusion-free until 4 months as we monitored. If pleural effusion occurs in a patient who has been administered a high-dose of amlodipine, the possibility of an amlodipine related adverse drug event should be considered.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

ETHICS STATEMENT
The authors confirm that the ethical policies of the journal, as notes on the journal’s author guidelines page, have been adhered to. No ethical approval was required as this is a description of the diagnosis and treatment of one case and no experimentation was conducted on the treated dog.

AUTHOR CONTRIBUTIONS
Writing-original draft and writing-review & editing: Hee-Won Jang. Conceptualization, visualization, writing-original draft, and writing-review & editing: Su-Min Park. Investigation: Seo-young Hwang. Visualization and investigation: Kyuyong Kang. Investigation: Mincheol Choi, Ju-Hyun An, and Hyung-Kyu Chae. Conceptualization, supervision, writing-original draft, writing-review & editing, and visualization: Ye-In Oh. Conceptualization, supervision, and writing-review & editing: Hwa-Young Youn.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, [HY Youn], upon reasonable request.

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