Sudden death following oral administration of flecainide to horses with naturally occurring atrial fibrillation.

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INTRODUCTION

Atrial fibrillation is the most common arrhythmia associated with poor performance in the horse. Quinidine has been historically the drug of choice for treating atrial fibrillation in horses due to its high efficacy (Reef et al., 1988). However, quinidine administration is associated with a range of cardiac and extra-cardiac side effects which are dose-dependent. Flecainide acetate is a class Ic antiarrhythmic drug which has been used in humans to treat atrial fibrillation. Flecainide does not cause the range of adverse effects observed following administration of quinidine. The pharmacokinetics of intravenous and oral administration of flecainide to horses has been determined (Ohmura et al., 2000, 2001) and flecainide has been shown to be effective in converting experimentally-induced and naturally-occurring cases of atrial fibrillation in the horse (Ohmura et al., 2000; Risberg and McGuirk, 2006). This report describes two cases of sudden death following oral administration of flecainide acetate to treat chronic, naturally-occurring atrial fibrillation. The horses had both previously been treated unsuccessfully with quinidine sulphate.

CASE DETAILS

The first horse was a 6 yo Thoroughbred racehorse which had a history of 2 previous episodes of atrial fibrillation over 18 months which had been successfully converted using quinidine, but failed to convert during a third episode. The second horse was a 4 yo Standardbred pacer in which quinidine had been unsuccessful in converting atrial fibrillation to sinus rhythm. Both horses were otherwise clinically normal, were racing and had histories of poor performance during race starts. In both cases, quinidine administration was discontinued due to the risk of onset of adverse effects associated with the accumulation of quinidine in serum at toxic concentrations. As the fibrillation was continuing, it was decided to attempt to convert to sinus rhythm using flecainide acetate, which was considered to be safer when administered to horses. Table 1 summarises the doses of quinidine and flecainide administered to the two horses.

Table 1: Details of quinidine sulphate (QS) and flecainide acetate (FA) treatment

Case	Total QS dose (time period)	No. doses QS administered	Total FA dose (time period)	No. Doses FA administered	Dose rate FA administered
1[a]	60 g (10 h)	6 x 10 g	-	-	-
1[b]	34 g (4 h)	2 g Test + 3 x 11 g	-	-	-
1[c]	32 g (4 h)	2 x 12 g; 1 x 8 g	6.6 g (4 h 50 min)	3 x 2.2 g	4.07 mg/kg q2h
2	25.6 g (8 h 20 min)	4 x 6.4 g	5.4 g (6 h 15 min)	3 x 1.8 g	4.05 mg/kg q2h

[a]July, 2005; [b]October, 2005; [c]February, 2007

The horses were monitored closely during treatment and showed no clinical signs of toxicity or changes in surface ECG. However, both horses collapsed and died suddenly after only 3 doses of flecainide and without any premonitory signs. Post-mortem examination of the hearts revealed no gross abnormalities.

DISCUSSION

This is the first published report of fatalities following administration of flecainide to horses. Flecainide has been associated with incidences of sudden death in asymptomatic human patients (Siebels et al., 1993). Sudden death without any detectable cause is rare in horses. Horses with long-standing atrial fibrillation are less likely to convert to sinus rhythm and are also more likely to revert to fibrillation after treatment. In human medicine type 1c antiarrhythmics such as flecainide have been reserved for conversion of tachyarrhythmias resistant to conversion with other drugs. Flecainide was chosen as a treatment for atrial fibrillation in the two cases described here as previous treatment with quinidine sulphate had been unsuccessful, and because flecainide is reported to be free of the extra-cardiac side effects observed during treatment with quinidine.
There was no evidence of underlying cardiac disease detected in either of the two horses described here either during ante mortem echocardiographic examinations or during post mortem examination. It is likely that the fatal outcomes observed here were due to direct effects on the heart at a membrane level in myocardial cells and conducting tissues.

The dose of flecainide acetate administered in the two cases described was within range determined to be safe and efficacious by Ohmura et al. (2000, 2001). The reported signs of flecainide toxicity include ECG changes (QRS and QT interval prolongation), ventricular arrhythmias, hypotension, agitation and mild abdominal discomfort (Ohmura et al., 2000,2001; van Loon et al., 2004; Risberg and McGuirk, 2006; Birettoni et al., 2007). In several cases, adverse effects were observed despite serum levels being within the determined "safe" range. In most cases, the observed adverse effects resolved following temporary cessation of treatment. In neither of the two cases reported here were any of the recognised signs of flecainide toxicity observed prior to the sudden death. We must therefore consider possible mechanisms for interaction between quinidine and flecainide that may account for the fatal outcomes.

The pharmacokinetics of orally-administered quinidine are quite variable (McGuirk et al. 1981 Bouckaert et al., 1994) thus it was possible that in the two cases reported here there were significant plasma levels of quinidine remaining in the horses at the time flecainide was administered (12-24 hours after administration of the last dose of quinidine), allowing cumulative effects of the drugs to be manifested. There are several mechanisms by which quinidine may have potentiated the fatal flecainide toxicity observed. Renal excretion is the primary route of flecainide elimination, with the remainder metabolised in the liver by a cytochrome P450 enzyme (Haefeli et al., 1990). Quinidine is a potent inhibitor of cytochrome P450 enzyme activity in the liver (Halpert et al., 1994). Furthermore, quinidine has been shown to decrease the renal clearance of digoxin via decreased glomerular filtration (Parraga, et al., 1995). Thus the pharmacokinetics of flecainide that have been established in healthy horses (Ohmura et al., 2000, 2001) may be altered somewhat in horses with significant serum concentrations of quinidine present, thus accounting for the accumulation of fatally toxic levels of flecainide.

An alternative explanation for the fatal toxicity observed here is that there were cumulative effects of the residual quinidine and flecainide on the heart. Both drugs are potent proarrhythmics due to lengthening of the QRS and QT intervals via Na^+ and K^+ blockade (Roden, 2001), and can cause dangerous dysrhythmias (Reef et al., 1988; van Loon et al., 2004; Risberg & McGuirk, 2006). The pharmacokinetics of quinidine and flecainide are less variable following intravenous administration compared with oral administration (McGuirk et al., 1981 ; Ohmura et al., 2000, 2001), and therefore the risk of cumulative effects of the drugs may be lessened by intravenous administration. van Loon et al. (2004) administered quinidine sulphate (22 mg/kg po q2 h) to 9 horses after unsuccessful attempts to convert naturally-occurring atrial fibrillation with intravenous flecainide. Quinidine treatment was successful in converting 8 out of 9 horses and minimal adverse effects were observed. In their cases, quinidine was administered within 5 days of flecainide treatment, and as the flecainide was administered intravenously, it was unlikely that significant levels were present in the horses at the time of quinidine administration.

Neither of the two horses reported here had converted to sinus rhythm following three doses of flecainide. This was in accordance with other reports, which have demonstrated that the efficacy of the drug is poor in horses with naturally-occurring or chronic atrial fibrillation (van Loon et al. 2004; Birettoni et al., 2007).

CONCLUSION & CLINICAL RELEVANCE

This is the first report of fatalities following the administration of flecainide acetate to horses. Although the precise mechanism(s) leading to the fatal outcomes have not been elucidated, careful consideration should be given to the oral administration of two proarrhythmic drugs within a short time period. These cases also further demonstrate the poor efficacy of flecainide in treating chronic or naturally-occurring cases of atrial fibrillation in the horse.

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