Effects of imidazoline and nonimidazoline alpha-adrenergic agents, including xylazine, medetomidine, yohimbine, tolazoline, and atipamezole, on aggregation of bovine and equine platelets

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Objective—To investigate effects of various imidazoline and nonimidazoline α-adrenergic agents on aggregation and antiaggregation of bovine and equine platelets.

Sample—Blood samples obtained from 8 healthy adult cattle and 16 healthy adult Thoroughbreds.

Procedures—Aggregation and antiaggregation effects of various imidazoline and nonimidazoline α-adrenergic agents on bovine and equine platelets were determined via a turbidimetric method. Collagen and ADP were used to initiate aggregation.

Results—Adrenaline, noradrenaline, or α-adrenoceptor agents alone did not induce changes in aggregation of bovine or equine platelets or potentiate ADP- or collagen-induced platelet aggregation. Adrenaline and the α₂-adrenoceptor agonist clonidine had an inhibitory effect on ADP- and collagen-induced aggregation of bovine platelets. The α₂-adrenoceptor antagonists phentolamine and yohimbine also inhibited collagen-induced aggregation of bovine platelets. Noradrenaline, other α-adrenoceptor agonists (xylazine, oxymetazoline, and medetomidine), and α-adrenoceptor antagonists (atipamezole, idazoxan, tolazoline, and prazosin) were less effective or completely ineffective in inhibiting ADP- and collagen-induced aggregation of bovine platelets. The imidazoline α₂-adrenoceptor agonist oxymetazoline submaximally inhibited collagen-induced aggregation of equine platelets, and the α₂-adrenoceptor antagonist idazoxan, along with phentolamine and yohimbine, also inhibited collagen-induced aggregation of equine platelets. The imidazoline compound antazoline inhibited both ADP- and collagen-induced aggregation of equine platelets.

Conclusions and Clinical Relevance—Several drugs had effects on aggregation of platelets of cattle and horses, and effective doses of ADP and collagen also differed between species. The α₂-adrenoceptor agonists (xylazine and medetomidine) and antagonists (tolazoline and atipamezole) may be used by bovine and equine practitioners without concern for adverse effects on platelet function and hemostasis. (Am J Vet Res 2013;74:395–402)
ole α2-adrenoceptor agonist, has a complex effect on platelets. For example, clonidine binds with high affinity to α2-adrenoceptors on platelets but induces only limited platelet aggregation, which is in contrast to the effect of endogenous agonists such as adrenaline.1–3 In addition, clonidine potentiates ADP-induced aggregation of human platelets but has inhibitory activity against adrenaline- and noradrenaline-induced platelet aggregation.9,10 Although the mechanism underlying these conflicting actions of clonidine is unclear, it has been suggested that imidazole compounds may interact with non-α2-adrenoceptor binding sites on platelets.17–19 Two clonidine-related drugs have been reported to inhibit platelet adenylate cyclase through non-α2-adrenoceptor mechanisms because their effects were not blocked by yohimbine.20 Moreover, clonidine-displacing substance, which was extracted from bovine brain tissue,21 was recognized as a noncatecholamine derivative drugs that control platelet aggregation may have clinical benefits, such as for a hypercoagulation state accompanied by hypercatecholaminemia because catecholamines have a stimulatory effect on platelet aggregation.1–3 The purpose of the study reported here was to investigate aggregation and antiaggregation effects of various imidazoline or nonimidazoline α2-adrenergic agents on bovine and equine platelets.

Materials and Methods

Sample—Blood samples for use in the study were collected from 8 healthy adult cattle (5 Japanese Black cattle and 3 Holsteins) and 16 healthy adult Thoroughbreds (12 geldings and 4 mares). For experiments on ADP- and collagen-induced platelet aggregation, jugular blood samples were collected into plastic syringes that contained 3.5% sodium citrate solution (1 part anticoagulant:9 parts blood). Blood samples were centrifuged at 100 to 120 × g for 15 minutes to obtain PPP. The PPP was obtained by centrifugation of PRP at 1,500 × g for 15 minutes. The final platelet count was adjusted to 25 to 30 × 105 platelets/μL via dilution with autologous PPP. The study protocol was approved by the Animal Research Committee of Tottori University.

Aggregation experiments—Platelet aggregation experiments were performed as previously described.33–34 Briefly, a turbidimetric method was used. Percentage aggregation was determined after addition of aggregation agents and was standardized via the assumption that PPP and PRP represented 100% and 0% light transmission, respectively. An aliquot (200 μL) of PRP was placed in an aggregometer at 37°C, and then an aliquot (22 μL) of each aggregation agent (l-adrenaline, l-noradrenaline, antazoline HCl, clonidine HCl, idoxazol HCl, oxymetazoline HCl, prazosin HCl, tolazoline HCl, yohimbine HCl, phentolamine mesylate, atipamezole HCl, medetomidine HCl, xylazine HCl, ADP, and collagen) was added to the PRP 0.5 to 1 minute later. Adrenaline and noradrenaline were dissolved in 0.04M HCl solution and then diluted with saline (0.9% NaCl) solution. Prazosin was dissolved in sterile distilled water and then diluted with sterile saline solution. All other drugs were dissolved in saline solution. In addition, saline solution was used throughout as a negative control agent.

To examine the stimulatory or inhibitory effects of α2-adrenergic agents on ADP- or collagen-induced aggregation, α2-adrenergic agents were added 1 minute before the addition of ADP or collagen. Maximum percentage aggregation during the 10-minute interval after the addition of ADP or collagen was recorded.

Statistical analysis—All data were expressed as the mean ± SE; each mean represented results for 5 animals. Statistical analysis was performed with commercially available software. A 1-way ANOVA followed by the Dunnett post hoc test was used for intragroup comparisons of concentration-related aggregation. For the inhibitory effect of agents on platelet aggregation, IC50 was determined from the concentration-response curve. An ANOVA was used to compare IC50 values. Depending on the F value, the Student t test or Wilcoxon–Mann–Whitney test was used to determine significance. Differences were considered significant at values of P < 0.05

Results

Aggregation effects of α2-adrenergic agents on bovine platelets—Adrenaline, noradrenaline, oxymetazo-
line, clonidine, medetomidine, xylazine, yohimbine, phen tolamine, atipamezole, idazoxan, tolazoline, and praz osin at concentrations from 0.1 nmol/L to 100 µmol/L did not stimulate aggregation of bovine platelets (data not shown).

Aggregation effects of ADP or collagen on bovine and equine platelets—Both ADP and collagen induced aggregation of bovine and equine platelets in a dose-dependent manner. In bovine platelets, the aggregation effect of ADP at concentrations exceeding 1 µmol/L or collagen at concentrations exceeding 5 µg/mL was significantly different from values for the control (saline solution) agent (Figure 1). On the basis of these results, examination of the stimulatory effects of α-adrenergic agents on ADP- or collagen-induced platelet aggregation would necessitate a concentration of ADP (2 µmol/L) or collagen (3 µg/mL) that caused almost submaximal aggregation (<25%) to induce platelet aggregation because these concentrations of ADP and collagen induced optimal aggregation responses in most platelet preparations. In contrast, a concentration of ADP (20 µmol/L) or collagen (10 µg/mL) that induced almost complete platelet aggregation (>80% aggregation) was chosen to examine the inhibitory effects of α-adrenergic agents on ADP- or collagen-induced platelet aggregation.

Similarly, the aggregation effect in equine platelets at concentrations of ADP exceeding 0.5 µmol/L or collagen exceeding 1.5 µg/mL was significantly different from values for the control agent (Figure 1). A concentration of ADP (0.5 µmol/L) or collagen (1.5 µg/mL) that induced almost submaximal aggregation (approx IC25) was chosen to induce platelet aggregation because these concentrations of ADP and collagen induced optimal aggregation responses in most equine platelet preparations.

![Figure 1](image.png)

**Figure 1**—Mean ± SE percentage aggregation for ADP (A and B) and collagen (C and D) on bovine (A and C) and equine (B and D) platelets in citrated plasma. Each mean ± SE represents results for 5 animals. In addition, saline (0.9% NaCl) solution was included as a negative control agent. *Value differs significantly (P < 0.05; 1-way ANOVA followed by the Dunnett post hoc test) from the value for the saline solution.

The imidazoline α2-adrenoceptor agonist clonidine (1 to 100 µmol/L) significantly inhibited (by >50%) high-dose collagen-induced aggregation of bovine platelets (Figure 3; Table 1). The imidazoline α1-adrenoceptor antagonist phentolamine and the nonimidazoline α1-adrenoceptor antagonist yohimbine (10 to 100 µmol/L) also had an inhibitory effect of >50% on the high-dose collagen-induced platelet aggregation. The remaining α1-adrenoceptor agents did not have a clear effect on collagen-induced aggregation of bovine platelets.
The IC_{50} values obtained for the inhibition of high-dose collagen–induced aggregation of bovine platelets were summarized (Table 1). The IC_{25} and IC_{50} values were not attained for noradrenaline, xylazine, oxymetazoline, medetomidine, atipamezole, idazoxan, tolazoline, or prazosin. The inhibitory potencies (based on the IC_{50} values) of phentolamine were 4- to 11-fold as high as those of adrenaline, clonidine, and yohimbine.

Effects of imidazoline and nonimidazoline α-adrenoceptor agents on ADP- or collagen-induced aggregation of equine platelets—Concentration–effect curves of imidazoline and nonimidazoline α-adrenoceptor agents on ADP (0.5 µmol/L) or collagen (1.5 µg/mL)-induced aggregation of equine platelets in citrated plasma were plotted (Figure 4). Adrenaline, noradrenaline, and 4 α-adrenoceptor agonists (xylazine, oxymetazoline, clonidine, and medetomidine) were ineffective against ADP-induced aggregation of equine platelets. Four α-adrenoceptor antagonists (atipamezole, idazoxan, tolazoline, and prazosin) also were ineffective against ADP-induced aggregation of equine platelets, whereas yohimbine and phentolamine were effective at the highest concentrations evaluated. The imidazoline compound antazoline, which is devoid of α-adrenergic activity, was effective at a concentration of 100 µmol/L against ADP-induced platelet aggregation.

In contrast with results for ADP-induced platelet aggregation, inhibitory activity by the agents was clearly evident on collagen-induced aggregation of equine platelets. Noradrenaline, xylazine, medetomidine, and oxymetazoline caused incomplete inhibition of collagen-induced aggregation of equine platelets only at the highest concentrations evaluated. The imidazoline agent antazoline (1 to 100 µmol/L) significantly inhibited collagen-induced platelet aggregation in a dose-dependent manner (Figure 4; Table 2). The α_{2}-adrenoceptor antagonists phentolamine (1 to 100 µmol/L), idazoxan (10 to 100 µmol/L), and yohimbine (10 to 100 µmol/L) also inhibited collagen-induced ag-

![Figure 2](image-url)
Table 1—Mean ± SE potency of imidazoline and nonimidazoline α-adrenergic agents for the inhibition of aggregation of bovine platelets induced by a high dose of collagen (10 μg/mL).

<table>
<thead>
<tr>
<th>Agent</th>
<th>IC₅₀</th>
<th>IC₅₀</th>
<th>IC₅₀ ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>0.4 ± 0.3</td>
<td>5.4 ± 3.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.7 ± 0.2</td>
<td>3.0 ± 1.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>2.3 ± 1.0</td>
<td>0.7 ± 0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>16.1 ± 8.0</td>
<td>7.5 ± 3.01</td>
<td>10.7</td>
</tr>
</tbody>
</table>

* Each value represents results for 5 animals.

Table 2—Mean ± SE potency of imidazoline and nonimidazoline α-adrenergic agents for the inhibition of aggregation of equine platelets induced by collagen (1.5 μg/mL).

<table>
<thead>
<tr>
<th>Agent</th>
<th>IC₅₀</th>
<th>IC₅₀</th>
<th>IC₅₀ ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antazoline</td>
<td>0.9 ± 0.6</td>
<td>6.3 ± 3.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Xylazine</td>
<td>0.9 ± 0.7</td>
<td>8.3 ± 4.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Oxymetazoline</td>
<td>1.2 ± 0.8</td>
<td>6.5 ± 4.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>2.8 ± 2.06</td>
<td>7.3 ± 4.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Idazoxan</td>
<td>20.0 ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Each value represents results for 5 animals.
ND = Not determined.
See Table 1 for remainder of key.

The IC₅₀ and IC₅₀ values obtained for the inhibition of collagen-induced aggregation of equine platelets were summarized (Table 2). The IC₅₀ and IC₅₀ values were not attained for adrenaline, noradrenaline, xylazine, clonidine, medetomidine, atipamezole, tolazoline, or prazosin. The inhibitory potencies (based on the IC₅₀ values) of antazoline, phenololamine, idazoxan, and yohimbine were approximately equal for aggregation of equine platelets.

Discussion

The results of the study reported here confirmed and expanded on results of previous studies, which found that adrenaline alone did not induce a change in aggregation of bovine and equine platelets and did not potentiate ADP- or collagen-induced platelet aggregation. Furthermore, analysis of results of the present study also revealed that noradrenaline did not stimulate aggregation of bovine or equine platelets or potentiate the ADP- or collagen-induced aggregation of bovine and equine platelets. It can be presumed that both adrenaline and noradrenaline do not act as platelet agonists in cattle and horses.

In addition, other imidazoline or α-adrenoceptor agonists (clonidine, medetomidine, and xylazine) did not have any stimulatory or potentiating effects. Clonidine can induce, at least to a limited degree, aggregation in human platelets⁹ and can potentiate ADP-induced platelet aggregation.⁹ In the present study, clonidine did not potentiate ADP-induced aggregation in bovine or equine platelets, whereas oxymetazoline, an imidazoline adrenoeceptor agonist, only potentiated ADP-induced aggregation in bovine platelets and had no effect on aggregation in equine platelets. In another study⁴³ conducted by our research group, we found that clonidine did not potentiate ADP-induced platelet aggregation in dogs, but oxymetazoline caused a small potentiation of the ADP-induced platelet aggregation. Results of the present study, in combination with results of our previous study, highlight species-specific variation in the potentiation of platelet aggregation.

In the present study, adrenaline and the imidazoline α₁-adrenoceptor agonist clonidine had an inhibitory effect, rather than a stimulatory effect, on high-dose ADP- and high-dose collagen–induced aggregation in bovine platelets. Furthermore, the α₁-adrenoceptor antagonists phenololamine (imidazoline) and yohimbine (nonimidazoline) also significantly inhibited collagen-induced aggregation of bovine platelets by > 50%. Noradrenaline, other α₁-adrenoceptor agonists (xylazine, oxymetazoline, and medetomidine), and α₁-adrenoceptor antagonists atipamezole, idazoxan, tolazoline, and prazosin were less effective or ineffective in inhibiting collagen-induced aggregation of equine platelets.
cordance with the order of binding affinity values for α₂-adrenoceptors. Although the mechanism underlying the activity of these various agents is unclear, it appears logical to conclude that they interact with non-α₂-adrenoceptor binding sites on bovine platelets.

In contrast, the imidazole α₂-adrenoceptor agonist oxymetazoline inhibited collagen-induced aggregation of equine platelets by > 25%. Furthermore, the imidazole compound antazoline, which is devoid of α-adrenergic activity, also inhibited ADP-induced aggregation of equine platelets and strongly inhibited collagen-induced aggregation of equine platelets in a dose-dependent manner. It can be presumed that in horses (as well as in cattle), these agents exert a nonadrenergic effect via a non-α₂-adrenoceptor mechanism. The α₂-adrenoceptor antagonist idazoxan as well as phentolamine and yohimbine clearly had inhibitory activity against collagen-induced aggregation of equine platelets. Adrenaline, noradrenaline, and the remaining α₂-adrenoceptor agents were less effective or completely ineffective in inhibiting ADP- or collagen-induced aggregation of equine platelets. The drugs that had effects on equine platelets differed from those that had effects on bovine platelets; adrenaline and clonidine, both of which had a strong inhibitory effect on aggregation of bovine platelets, were ineffective on equine platelets. In addition, effective doses of ADP and collagen differed between platelets from cattle and horses. Analysis of these results suggests that there are critical species-specific differences (even between horses and cattle) in the platelets or in the reactivity of platelets, thus may have useful clinical applications in cattle and horses.

Mammalian platelets have a wide range of responses to adrenaline in part because adrenaline can act via excitatory α₂-adrenoceptors and inhibitory β-adrenoceptors. Adrenaline acts as a platelet agonist in humans, with a mean receptor density of 258 α₂-adrenoceptors/platelet and 66 β₁-adrenoceptors/platelet (α₂-adrenoceptor:β₁-adrenoceptor ratio, 3.91). It has been suggested that the α₂-adrenoceptor:β₁-adrenoceptor ratio determines whether adrenaline acts as a platelet agonist. Although data on platelet adrenoceptor density is not available for cattle or horses, it can be speculated that a 100 µmol/L dose of adrenaline in the present study stimulated β₁-adrenoceptors, which inhibited platelet aggregation. This does not exclude the possibility that adrenaline inhibited ADP-induced aggregation of bovine platelets in a dose-dependent manner. In the present study, certain imidazoline agents inhibited ADP- or collagen-induced aggregation of bovine or equine platelets. There is no evidence of imidazoline receptors, in addition to α₂- and β₁-adrenoceptors, on bovine and equine platelets. We presume that the binding sites mediating these nonadrenergic effects may be the imidazoline receptors that have been identified on human platelets.25,26 Future investigations to identify and elucidate the function of these receptors is warranted. Nevertheless, it is possible that the imidazoline structure is involved, in part, in the inhibition of adrenaline-potentiated aggregation and that imidazoline adrenoceptor agents also interact with atypical nonadrenergic receptors.

A variety of drugs are clinically available that have activity at α₂-adrenoceptors. In veterinary medicine, including bovine and equine practice, the α₂-adrenoceptor agonists xylazine, medetomidine, and clonidine may be used for sedation, analgesia, and premedication for general anesthesia, and the α₂-adrenoceptor antagonists atipamezole and yohimbine are used for the reversal of the effects of the α₂-adrenoceptor agonists. In the present study, the effects of clinically used α₂-adrenoceptor agents on aggregation of platelets from healthy cattle and horses were evaluated. In combination with pharmacokinetic data after systemic administration of xylazine and medetomidine at clinically recommended doses in cattle and horses,46-47 results for the present study indicated that the α₂-adrenoceptor agonists xylazine and medetomidine at estimated effective blood concentrations may be used by bovine and equine practitioners without concern for adverse effects on platelet function and hemostasis.

On the other hand, clonidine may be used safely for adverse platelet reactions on hemostasis in horses because it has no stimulatory effect on equine platelets, whereas a relatively high dose of clonidine may inhibit ADP- and collagen-related hemostasis in cattle. The α₂-adrenoceptor antagonists yohimbine and phentolamine may also have inhibitory effects on bovine and equine hemostatic systems for certain events, such as blood vessel damage and collagen exposure. Yohimbine is ineffective in antagonizing xylazine-induced sedation and has a narrow therapeutic safety margin in cattle; therefore, it is proposed that tolazoline, an imidazoline α₂-selective antagonist, could be used in cattle as a substitute for yohimbine.48-50 In addition, the present study revealed that tolazoline and atipamezole have no stimulatory effects on bovine and equine platelets and thus may have useful clinical applications in cattle and horses.

In the present study, adrenaline, noradrenaline, and α₂-adrenoceptor agents alone did not induce a change in aggregation in bovine or equine platelets or potentiate platelet aggregation induced by ADP or collagen. It is suggested that the α₂-adrenoceptors on bovine and equine platelets may not be involved in the mediation of platelet aggregation, at least when stimulated by ADP or collagen, and that nonadrenergic imidazoline receptors, similar to receptors described in human platelets, may also be present on bovine and equine platelets. Furthermore, analysis of the results of the present study revealed that clinical doses of α₂-adrenoceptor agonists (xylazine and medetomidine) and α₂-adrenoceptor antagonists (tolazoline and atipamezole) may be used in bovine and equine practice without concern for adverse effects on platelet function and hemostasis. Various drugs had differing efficacy on platelets of cattle and horses, and the effective doses of ADP and collagen also differed between cattle and horses. Analysis of these results suggests that there are critical species-specific differences in the platelets or in the reactivity of platelets, even between horses and cattle.

a. MCM Hema tracer 804, LMS Co Ltd, Tokyo, Japan.
b. Tokyo Kaisei Industries Co, Tokyo, Japan.
c. Sigma Chemical Co, St Louis, Mo.
d. Ciba-Geigy Corp, Hyogo, Japan.e. Farmos Group Ltd, Turku, Finland.
f. Bayer, Leverkusen, Germany.
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pha 2-adrenoceptor ligands at alpha2A and 5-HT1A receptors, 
the antagonist, atipamezole, and the agonist, dexametomidine,

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