Effects of BQ-788, an ETB receptor antagonist, on amitriptyline-induced cardiovascular toxicity in rats

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Introduction

- Most common cause of TCA poisonings
- The second cause of the deadly poisonings by antidepressants
- Hypotension and QRS prolongation
  - Alfa-1 adrenergic receptor blockade,
  - Noradrenaline re-uptake inhibition,
  - Fast sodium channel blockade in the heart
- Other mechanisms of poisoning with TCAs
  - Nitric oxide secretion (NO)
  - Adenosine receptors

Hypotension and QRS prolongation

Material & Methods

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Measured parameters</th>
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<tbody>
<tr>
<td>Amtriptyline, TCA</td>
<td>MAP= (SP+2DP)/3</td>
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<tr>
<td>BQ-788, ETB receptor antagonist</td>
<td>Heart rate (HR)</td>
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<tr>
<td>DMSO</td>
<td>QRS duration</td>
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Biorex MP150.0 DC, 35481556A, USA
Braun, Perfusor Compact S, Germany

| Table 1. The effects of BQ-788 bolus (10 nmol/w) on MAP, HRs and QRS duration (n=3) |
|----------------------------------|---------------------------------|
| POST 5 min | POST 10 min | POST 15 min | POST 20 min | POST 25 min | POST 30 min |
| 114.8±10.9 | 116.1±14.8 | 117.8±11.4 | 117.8±17.0 | 118.8±12.3 | 118.9±16.7 | 119.8±19.8 |
| HR (bpm)   | 119.0±12.8 | 119.0±12.7 | 119.1±12.3 | 117.5±11.0 | 117.0±11.1 | 116.1±12.6 | 114.8±11.5 |
| MAP (mmHg) | 125.0±17.0 | 125.0±21.0 | 125.0±15.0 | 125.0±20.0 | 125.0±15.0 | 125.0±15.0 | 125.0±15.0 |

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Preliminary study

AIM

to investigate the effects of BQ-788, an ETB receptor antagonist, on amitriptyline-induced

- Mean Arterial Pressure (MAP),
- Heart Rate (HRs),
- QRS prolongation

BQ-788 did not cause any significant change in baseline levels of MAP, HRs and QRS duration within thirty minutes.
Results

<table>
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<th>Control (n=8)</th>
<th>BQ-788 (n=6)</th>
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<td>% inhibition MAP</td>
<td>48.7±1.1%</td>
<td>58.3±1.8%</td>
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Figure 1: The effects of 5% dextrose or BQ-788 on amitriptyline induced (A) MAP, (B) QRS duration and (C) HRs. (*: BQ-788; ■: 5% dextrose). (*): p<0.05, (***): p<0.001 versus control.

Discussion 1

**Hypotension**

- BQ-788 improved the amitriptyline-induced hypotension
  - Increased ET-1 levels in circulation
  - Increased ET-1 levels might improve hypotension by enhancing Ca++ influx through the L-type calcium channels.
  - Increased endogenous catecholamine releasing activity by endothelin.
  - Inhibition of NO secretion from endothelium.

Discussion 2

**Heart rate**

- BQ-788 improved the amitriptyline-induced bradycardia
  - BQ-788 might have beneficial effect on HRs via sympathoexcitatory effect of endothelin
  - Sympathoexcitatory effects of endothelins in normotensive and hypertensive patients were demonstrated through ETA receptors

Discussion 3

**QRS prolongation**

- BQ-788 improved the amitriptyline-induced QRS prolongation
  - A tetrodotoxin-resistant (TTX-R) voltage-gated Na+ current in human cardiac tissue (hH1, Nav 1.5) was demonstrated to be enhanced by ET-1
  - BQ-788 might increase Na+ current in the heart.

Conclusion

- ETα receptor antagonists may have beneficial effects in cardiovascular toxicity induced by amitriptyline
  - ETα receptors might play a role in amitriptyline-induced cardiovascular toxicity.
  - BQ-788 might improve amitriptyline-induced decrease in MAP and HRs, and QRS prolongation by physiological antagonism.

Future studies

- The role of ETα receptors in amitriptyline-induced cardiovascular depression
- The role of NO secretion from endothelial cells and the contribution of ETα receptors in amitriptyline-induced vasodilatation in rat thoracic aorta.
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