EFFECT OF CARBAMAZEPINE ON THE SPONTANEOUS BEATING OF ISOLATED GUINEA PIG ATRIA

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ABSTRACT

Carbamazepine, a drug effective in pain, seizure, and affective disorders, was studied for its effects and toxicity on spontaneously beating isolated guinea pig atria. Carbamazepine (20-50 μg/mL) has a negative chronotropic effect on atria, without any significant effect on contractile force. The most significant effect (12.5%) was seen with 30 μg/mL of carbamazepine on atria. With higher doses (>30 μg/mL) carbamazepine produced toxic effects which resulted in atrial standstill. Pretreatment of atria with theophylline (5-50 μg/mL) prevented the negative chronotropic effect of carbamazepine (30 μg/mL). Three dose ratios of carbamazepine (1.33, 2, 2.33) in the presence of three different doses of theophylline (30, 50 and 60 μg/mL) were obtained. These results suggest that the negative chronotropic effect of carbamazepine and its toxicity may be due to its action as an agonist on adenosine A1 receptors and as an antagonist on A2 receptors of the atria. Moreover, using adenosine antagonists such as theophylline may overcome the toxic effect of carbamazepine on the heart. This may explain the reason for the interaction between carbamazepine and theophylline in clinical settings.


Keywords: Carbamazepine, isolated atria, theophylline, adenosine receptors.

INTRODUCTION

Carbamazepine is a tricyclic anticonvulsant drug. Its most pronounced clinical effect is in seizure disorders, paroxysmal pain syndromes and treatment of manic-depressive disorders. Carbamazepine is also effective in terminating digital-induced ventricular tachyarrhythmias. Carbamazepine blocks sodium channels at therapeutic concentrations and inhibits high-frequency repetitive firing in neurons in culture. It has also been shown that carbamazepine in therapeutic doses can interact with adenosine receptors. It has been suggested that the anticonvulsant properties of carbamazepine may be partially explained by an influence of this drug on adenosine receptors.

been shown that carbamazepine interacts competitively with adenosine-binding sites in the brain. It has been claimed that carbamazepine binds to A1 receptors completely and to A2 receptors partially at therapeutic levels. Derivatives may act as agonists of A1 receptors and antagonists of A2 receptors. Moreover, methylxanthines have stimulant and convulsant properties due to their action as antagonists on both A1 and A2 receptors. It has been shown that theophylline completely reverses the anticonvulsant action of carbamazepine. Carbamazepine also increases the severity of heart block caused by adenosine.

Adenosine receptors are G-protein coupled receptors and are divided into four subtypes, including A1, A2, A3, and A4, based on agonist actions of adenosine. A1 and A2 receptors are antagonized by xanthines, whereas A3 and A4 receptor are not. Stimulation of A1 recep-
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tors has been associated with inhibition of adenylyl cy-
clase, and activation of K+ currents as well as activation
of phospholipase C in some circumstances, and ion chan-
el regulation.3,12 A2 receptors stimulate adenylyl cy-
clase activity.13,12 Activation of A3 receptors also causes
the release of inflammatory mediators such as histamine
from mast cells.2 The physiologic role of A4 receptors
remains unclear.13 Adenosine has negative chronotropic
and dromotropic effects in patients with paroxysmal su-
praventricular tachycardia.10,17 These effects of adenos-
ine would be mediated by A1 receptor subtypes.8 By act-
ing on both the sinoatrial and atrioventricular nodes, ad-
enosine causes bradycardia and heart block.6 Adenosine
analogues have inhibitory effects in guinea pigs atria.4
Theophylline is a nonselective adenosine receptor an-
tagonist,6 Theophylline and carbamazepine reduce the
efficacy of each other when they are co-administered.5

The aim of the present study was to determine the
effects of carbamazepine on isolated heart, to find a way
to prevent the toxic effects of carbamazepine on the heart
and to explore the interactions between carbamazepine
and theophylline.

MATERIAL AND METHODS

Experimental protocol

Guinea pigs (300-700g) of either sexes were killed by a
sharp blow to the back of the neck. The hearts were
excised and placed in cool oxygenated Ringer Lock so-
lution of the following composition (gram per liter):
NaCl, 9; KCl, 0.42; CaCl2, 0.12; NaHCO3, 0.5; and glu-
cose, 1. The atria were dissected and isolated from other
tissues. The preparation was then mounted in a 20-mL
organ bath which contained Ringer Lock solution, gassed
with a mixture of 95% oxygen and 5% CO2, and main-
tained at a constant temperature of 36-37°C. A resting
tension of 1g was applied and kept constant by readjust-
ment during the equilibration period. The mechanical
activity was recorded isometrically by means of a Grass
701E polygraph. The preparation were allowed to equili-
brate 30 minutes before the use of drugs. The organ bath
solution was changed every 15 minutes during the equili-
bration period. Each time the volume of drug solution
added to the organ bath was 0.1 mL . In this study all
drug concentrations are indicated as milligram of drug
per milliliter of organ solution. Carbamazepine was dis-
solved in propylene glycol to which the tissues in the or-
gan bath were exposed (0.005 mL/mL) and had no sig-
ificant effect on the rate and force of contraction of iso-
lated atria. Theophylline was dissolved in distilled deion-
ized water. In each experiment six guinea pigs were used.

Statistical analysis

Responses were measured as percentage of basal lev-
els. Statistical significance was evaluated by the t-test
for paired and unpaired samples and P values of 0.05 or
less were considered to be significant.

Drugs

Carbamazepine, theophylline and propylene glycol
(Sigma, USA).

RESULTS

In order to determine the effects of carbamazepine
alone on spontaneously beating isolated guinea pig atria,
carbamazepine was added to the organ bath at concen-
trations of 2.5-40 µg/mL. At concentrations of 2.5-15
µg/mL, carbamazepine had no effect on spontaneously
beating isolated atria. At concentrations of 20-30 µg/mL
it decreased the rate of contraction (Fig. 3), without any
significant change in contractile force. At a concentra-
tion of 30 µg/mL it produced the most significant nega-
tive chronotropic effect (12.45%) on isolated atria
(p<0.025). At higher doses (30 µg/mL), carbamazepine
produced bradyarrhythmias which lead to atrial stand-
still.

In order to determine the effects of theophylline alone
on spontaneously beating isolated guinea pig atria, theo-
phylline was added to the organ bath at concentrations
of 2.5-60 µg/mL. Theophylline increased the rate and
force of contraction of isolated atria in a dose-depen-
dent manner (Figs. 1 and 2). Theophylline at a concen-
tration of 50 µg/mL produced the most potent inotropic
(86.64%) and chronotropic (21.15%) effects on isolated
atria.

Atria were pretreated with different doses of theo-
phylline (2.5-50 µg/mL). After an incubation period of
10 minutes, carbamazepine at a concentration of 30 µg/
ML, which showed the most significant negative chro-
notropic effect, was added to the organ bath. Then the
effects of carbamazepine (30 µg/mL) in the presence of
different doses of theophylline was investigated as well.
In this study theophylline prevented the negative chro-
notropic effect of carbamazepine (30 µg/mL) in a dose-
dependent manner (Fig. 3).

Three dose ratios of carbamazepine in the presence
of three different doses of theophylline were obtained.
Atria were pretreated with theophylline (30 µg/mL). After
an incubation period of 10 minutes, carbamazepine (20-
50 µg/mL) was added. The effective dose of car-
bamazepine in the presence of theophylline (30 µg/
ML) shifted from 30 µg/mL to 40 µg/mL and the dose
ratio was 1.33. The toxic dose of carbamazepine in the
presence of theophylline (30 µg/mL) shifted from 40 µg/
ML to 50 µg/mL (Fig. 4). Then the atria were pretreated
with theophylline (50 µg/mL) and after the incubation
period, different concentrations of carbamazepine (25-
Theophylline dose (µg/mL)

Fig. 1. Log dose-response curve of spontaneously beating isolated guinea pig atria to the inotropic effect of theophylline.

Theophylline dose (µg/mL)

Fig. 2. Log dose-response curve of spontaneously beating isolated guinea pig atria to the chronotropic effect of theophylline.

Theophylline dose (µg/mL)

Fig. 3. Log dose-response curve of spontaneously beating isolated guinea pig atria to the chronotropic effects of (□) carbamazepine alone, (●) theophylline in the presence of carbamazepine (30 µg/mL), and (▲) theophylline alone.

60 µg/mL were added. The effective dose of carbamazepine in the presence of theophylline (50 µg/mL) shifted from 30 µg/mL to 60 µg/mL and the dose ratio was 2. The toxic dose of carbamazepine in the presence of theophylline (50 µg/mL) shifted from 40 µg/mL to 70 µg/mL (Fig. 4). Finally, the atria were pretreated with theophylline (60 µg/mL) and after the incubation period, different concentrations of carbamazepine (40-80 µg/mL) were added. The effective dose of carbamazepine in the presence of theophylline (60 µg/mL) shifted from 30 µg/mL to 70 µg/mL and the dose ratio was 2.33. The toxic dose of carbamazepine in the presence of theophylline (60 µg/mL) shifted from 40 µg/mL to 80 µg/mL (Fig. 4).

DISCUSSION

It has been shown that the anticonvulsant properties of carbamazepine may be partially explained by an influence of this drug on adenosine receptors. It has been claimed that carbamazepine interacts competitively with adenosine-binding sites in the brain. It has also been shown that theophylline completely reverses the anticonvulsant action of carbamazepine. It has been suggested that carbamazepine acts as an agonist on A1 receptors and an antagonist on A2 receptors. In this study carbamazepine had a negative chronotropic effect on spontaneously beating isolated guinea pig atria. This is similar to the adenosine effect. Pretreatment of atria with theophylline (5-50 µg/mL), an unselective antagonist of adenosine receptors, prevented the negative chronotropic effect of carbamazepine. The negative chronotropic and dromotropic effects of adenosine are mediated by A1 receptor subtypes. Stimulation of A1 receptors causes inhibition of adenylyl cyclase and enhances potassium conductance which both lead to suppression of automaticity of the sinus node. Stimulation of A2 receptors activates adenylyl cyclase. Thus the antagonism effect on A2 receptors may lead to further inhibition of adenylyl cyclase which favors more suppression of the sinus node. The results may suggest that carbamazepine produces its negative chronotropic effect by acting as an agonist on A1 receptors and an antagonist on A2 receptors of isolated guinea pig atria. It is also suggested that theophylline, an unselective adenosine...
The results also showed that carbamazepine may have interaction with adenosine and intensify the toxic effects of adenosine when they are co-administered.

REFERENCES


A. Pousti and S. Bakhtiari


