Data in Brief 14 (2017) 440–452

Contents lists available at ScienceDirect

Data in Brief

journal homepage: www.elsevier.com/locate/dib

Data article

Data and calculus on isobolographic analysis to determine the antinociceptive interaction between calcium channel blocker and a TRPV1 blocker in acute pain model in mice

Juliana F. Silva [a], Manuella R. Palhares [a], Duana C. Santos [a], Cláudio A. Silva-Junior [a], Juliano Ferreira [b], Marcus V. Gomez [a], Célio J. Castro Junior [a,*]

[a] Department of Neurotransmitters, Institute of Education and Research, Santa Casa, Belo Horizonte, Minas Gerais 30150-240, Brazil
[b] Department of Pharmacology, Biological Sciences Center, Federal University of Santa Catarina, Florianópolis, Santa Catarina 80040-900, Brazil

ARTICLE INFO

Article history:
Received 16 June 2017
Received in revised form 27 June 2017
Accepted 25 July 2017
Available online 27 July 2017

ABSTRACT

Determining antinociceptive interaction between Phα1β toxin (a voltage gated calcium channel blocker) and SB366791 (selective TRPV1 antagonist) may have both clinical and mechanistic implications for the pain management. This data in brief article is associated to the research paper "Synergistic antinociceptive effect of a calcium channel blocker and a TRPV1 blocker in an acute pain model in mice". This material supports the isobolographic analysis performed with the above drugs and shows: data of the dose response curves of the agents given as single drug or combination regimens. Mathematics and statistical processing of dose response curves, proportion of drugs dosage to be used in the combination, calculus of theoretical additive DE_{20} dose as well as experimentally obtained DE_{20} are provided. It is also presented details of statistical comparison between theoretical and experimentally obtained DE_{20}.

DOI of original article: http://dx.doi.org/10.1016/j.lfs.2017.06.018
* Corresponding author.
E-mail address: celiojcjunior@gmail.com (C.J. Castro Junior).

http://dx.doi.org/10.1016/j.dib.2017.07.059
2352-3409/

Specifications Table

Subject area	*Biology*
More specific subject area	*Neuropharmacology, pain management*
Type of data	*Table, text file*
How data was acquired	*Experimental observation of nociceptive behavior in mice by using a chronometer.*
Data format	*Raw and analyzed*
Experimental factors	*Dose response curves for Single drug administration of combined drugs, given at the same of at different sites*
Experimental features	*Isobolographic analysis using a fixed proportion ratio of two drugs.*
Data source location	*N.A.*
Data accessibility	*Data is with this article.*

Value of the data

- *Data tables and calculus from this article may serves as a practical guide on isobolographic analysis for testing other drug regimens of even using different pain models.*
- *Determining the interaction index by isobolographic analysis provides a measure of the in vivo degree of interaction of two drugs for a specified effect.*
- *Data analysis presented in this article can be systematically compared to other data from probit analysis with analgesic drugs given in combination.*

1. Data

1.1. Summary of linear regression analyses for the agents administered alone

1.1.1. Intraplantar SB366791

See Table 1.

Table 1
Dose-effect data of SB366791 (i.p.) on capsaicin-induced nociception.

Dose	x_i	y_i	$x_i.y_i$	$(x_i-\bar{X})^2$
0.10	-1.00	8.86	-8.86	0.74
0.10	-1.00	-14.77	14.77	0.74
0.10	-1.00	-41.77	41.77	0.74
0.10	-1.00	38.29	-38.29	0.74
0.10	-1.00	37.43	-37.43	0.74
0.10	-1.00	-22.57	22.57	0.74
0.10	-1.00	-23.58	23.58	0.74
0.10	-1.00	0.81	-0.81	0.74
0.10	-1.00	-10.76	10.76	0.74
0.10	-1.00	-0.63	0.63	0.74
0.10	-1.00	-13.83	13.83	0.74
0.10	1.00	64.31	-64.31	0.74
0.10	-1.00	48.42	-48.42	0.74
0.10	-1.00	18.18	-18.18	0.74
0.40	-0.40	-13.08	5.23	0.07
0.40	-0.40	-23.21	9.28	0.07
0.40	-0.40	4.64	-1.86	0.07
0.40	-0.40	9.14	-3.66	0.07
0.40	-0.40	36.57	-14.63	0.07

Table 1 (*continued*)

Dose	x_i	y_i	$x_i.y_i$	$(x_i\text{-}\bar{X})^2$
0.40	-0.40	27.14	-10.86	0.07
0.40	-0.40	45.80	-18.32	0.07
0.40	-0.40	33.33	-13.33	0.07
0.40	-0.40	0.27	-0.11	0.07
0.40	-0.40	12.03	-4.81	0.07
0.40	-0.40	59.49	-23.80	0.07
1.00	0.00	-25.75	0.00	0.02
1.00	0.00	18.16	0.00	0.02
1.00	0.00	12.20	0.00	0.02
1.00	0.00	-1.90	0.00	0.02
1.00	0.00	17.72	0.00	0.02
1.00	0.00	25.32	0.00	0.02
1.00	0.00	2.53	0.00	0.02
1.00	0.00	5.06	0.00	0.02
1.00	0.00	-19.61	0.00	0.02
1.00	0.00	6.43	0.00	0.02
1.00	0.00	-12.06	0.00	0.02
1.00	0.00	50.79	0.00	0.02
1.00	0.00	29.37	0.00	0.02
1.00	0.00	15.08	0.00	0.02
1.00	0.00	44.44	0.00	0.02
1.00	0.00	31.75	0.00	0.02
2.00	0.30	26.58	7.97	0.19
2.00	0.30	70.46	21.14	0.19
2.00	0.30	53.59	16.08	0.19
2.00	0.30	22.86	6.86	0.19
2.00	0.30	40.86	12.26	0.19
2.00	0.30	13.43	4.03	0.19
2.00	0.30	13.28	3.98	0.19
2.00	0.30	22.49	6.75	0.19
2.00	0.30	52.85	15.85	0.19
2.00	0.30	-10.13	-3.04	0.19
6.00	0.78	30.62	23.89	0.85
6.00	0.78	65.31	50.94	0.85
6.00	0.78	17.07	13.32	0.85
6.00	0.78	84.28	65.74	0.85
6.00	0.78	25.95	20.24	0.85
6.00	0.78	23.42	18.27	0.85
6.00	0.78	18.99	14.81	0.85
6.00	0.78	6.33	4.94	0.85
6.00	0.78	60.13	46.90	0.85

Legend: Dose (nmol/site); x_i: Log of dose (nmol/site); y_i: (% of MEP); x_iy_i: product $x_i.y_i$; $(x_i\text{-}\bar{X})^2$: $(x_i - x_i \text{ average})^2$.
-Linear regression summary:
$\sum x = -8.38$; $\sum y = 1118.42$; N= 60; $\bar{X} = -0.1397$; $\bar{Y} = 18.64$; $\sum x^2 = 22.13$;
$\sum x.y = 185.67$; N.x.y = -156.20; $\bar{X}^2 = 0.0195$

$b = \frac{\sum xiyi - \bar{N}xy}{\sum xi^2 - \bar{N}x^2}$;

$a = \bar{y} - \bar{b}x$. thus b = 16.3 (slope) and a = 20.9 *(intercept)*
-Slope variance = $V(b) = \frac{s^2}{\Sigma(xi-X)2}$. wherein $s^2 = Q/(N\text{-}2)$ and $Q = \sum_{i=1}^{N}(yi-a-bxi)$
V(b) = 31.3
- Assessment if slope differs from 0:
$t_{slope} = b/\{V(b)\}^{1/2}$; t_{slope} = 2.91 which exceeds t-tabulated, thus slope differs from zero.
t_{table} (N-2 degrees of freedom; P=0.05; from t-distribution) = 1.96
- DE_{20} calculation: DE20 = (20 – a)/b (in log scale); DE20 = –0.056 or 0.88 nmol/site
- Variance of DE_{20} (V_{DE20}); = s^2 / b^2 [$1/N + (x^1-\ddot{x})^2 / S_{xx}$]; V_{DE20} = 0.042 (in log scale)

1.1.2. Intraplantar Phα1β

See Table 2.

Table 2
Dose-effect data Phα1β (i.p.) on capsaicin-induced nociception.

Dose	x_i	y_i	x_iy_i	$(x_i-\bar{X})2$
0.01	-2.00	19.51	-39.02	1.00
0.01	-2.00	27.44	-54.88	1.00
0.01	-2.00	46.34	-92.68	1.00
0.01	-2.00	0.33	-0.66	1.00
0.01	-2.00	6.23	-12.46	1.00
0.01	-2.00	-36.30	72.61	1.00
0.01	-2.00	20.49	-40.98	1.00
0.01	-2.00	12.31	-24.63	1.00
0.03	-1.52	18.90	-28.73	0.27
0.03	-1.52	31.71	-48.20	0.27
0.03	-1.52	18.69	-28.41	0.27
0.03	-1.52	44.92	-68.28	0.27
0.03	-1.52	7.54	-11.46	0.27
0.03	-1.52	30.51	-46.38	0.27
0.03	-1.52	30.51	-46.38	0.27
0.03	-1.52	-15.59	23.70	0.27
0.10	-1.00	64.63	-64.63	0.00
0.10	-1.00	26.22	-26.22	0.00
0.10	-1.00	50.61	-50.61	0.00
0.10	-1.00	48.17	-48.17	0.00
0.10	-1.00	8.20	-8.20	0.00
0.10	-1.00	14.10	-14.10	0.00
0.10	-1.00	35.74	-35.74	0.00
0.10	-1.00	37.05	-37.05	0.00
0.10	-1.00	25.84	-25.84	0.00
0.10	-1.00	29.18	-29.18	0.00
0.10	-1.00	38.53	-38.53	0.00
0.30	-0.52	54.27	-28.22	0.23
0.30	-0.52	44.51	-23.15	0.23
0.30	-0.52	43.61	-22.68	0.23
0.30	-0.52	20.00	-10.40	0.23
0.30	-0.52	30.49	-15.86	0.23
0.30	-0.52	45.88	-23.86	0.23
0.30	-0.52	55.23	-28.72	0.23
0.30	-0.52	5.12	-2.66	0.23
0.50	-0.30	67.68	-20.30	0.49
0.50	-0.30	68.29	-20.49	0.49
0.50	-0.30	62.20	-18.66	0.49
0.50	-0.30	62.80	-18.84	0.49
0.50	-0.30	65.85	-19.76	0.49
0.50	-0.30	30.49	-9.15	0.49
0.50	-0.30	35.08	-10.52	0.49
0.50	-0.30	41.64	-12.49	0.49

Table 2 (*continued*)

Dose	x_i	y_i	x_iy_i	$(x_i–\bar{X})2$
0.50	-0.30	41.64	-12.49	0.49
0.50	-0.30	41.87	-12.56	0.49
0.50	-0.30	58.57	-17.57	0.49
0.50	-0.30	56.57	-16.97	0.49

Legend: Dose (nmol/site); x_i: Log of dose (nmol/site); y_i: (% of MEP); x_iy_i: product $x_i.y_i$; $(x_i–\bar{X})^2$: (x_i –x_i averaged)^2.
Linear regression summary:
$\sum x$= -46.92; $\sum y$= 1589.6; N= 47; $\bar{X}$= -0.99; $\bar{Y}$= 33.82; $\sum x^2$ = 64.72;
$\sum x.y$= -1175.24; N.x.y = -1586.9; $\bar{X}^2$= 0.99

$$b = \frac{\sum xiyi - \bar{N}xy}{\sum xi^2 - \bar{N}x^2};$$

$a = \bar{y} - \bar{b}x$. thus b = 23.^{2} (slope) and a = 57.1 *(intercept)*
Slope variance = $V(b) = \frac{s^2}{\Sigma(xi-\bar{X})2}$. wherein s^2 = $Q/(N\text{-}2)$ and $Q = \sum_{i=1}^{N}(yi - a - bxi)$
V(b) = 18.1
- Assessment if slope differs from 0:
t_{slope} = b/{V(b)}$^{1/2}$; t_{slope} = 5.40 which exceeds t-tabulated, thus slope differs from zero
t_{table} (N-2 degrees of freedom; P=0.05; from t-distribution) = 1.96
- DE_{20} calculation: DE20 = (20 – a)/b (in log scale); DE20 = −1.60 or 0.025 nmol/site
- Variance of DE_{20} (V_{DE20}); = s^2 / b^2 [1/N + $(x^1–\ddot{x})^2$/ S_{xx}]; V_{DE20} = 0.025 (in log scale)

1.1.3. *Intrathecal Phα1β*

See Table 3.

Table 3
Dose-effect data of Phα1β (i.t.) on capsaicin-induced nociception.

Dose	x_i	y_i	x_iy_i	$(x_i- \bar{X})^2$
0.0003	-3.52	39.54	-139.20	2.47
0.0003	-3.52	-25.58	90.05	2.47
0.0003	-3.52	31.40	-110.50	2.47
0.0003	-3.52	-4.65	16.37	2.47
0.0003	-3.52	41.29	-145.30	2.47
0.0003	-3.52	13.11	-46.15	2.47
0.0003	-3.52	4.50	-15.84	2.47
0.0003	-3.52	-0.98	3.44	2.47
0.0003	-3.52	13.82	-48.64	2.47
0.0003	-3.52	12.88	-45.34	2.47
0.0003	-3.52	-1.17	4.12	2.47
0.0003	-3.52	20.38	-71.72	2.47
0.0003	-2.52	50.00	-126.00	0.33
0.003	-2.52	24.63	-62.06	0.33
0.003	-2.52	39.55	-99.67	0.33
0.003	-2.52	34.18	-86.13	0.33
0.003	-2.52	65.40	-164.80	0.33
0.003	-2.52	20.37	-51.33	0.33
0.003	-2.52	24.07	-60.67	0.33
0.003	-2.52	17.44	-43.95	0.33
0.003	-2.52	23.26	-58.60	0.33
0.003	-2.52	20.93	-52.74	0.33
0.003	-2.52	27.20	-68.55	0.33
0.003	-2.52	63.47	-159.90	0.33
0.003	-2.52	42.86	-108.00	0.33
0.003	-2.52	37.24	-93.84	0.33
0.01	-2.00	19.84	-39.68	0.00
0.01	-2.00	-30.95	61.91	0.00
0.01	-2.00	47.76	-95.52	0.00
0.01	-2.00	50.00	-100.00	0.00
0.01	-2.00	96.27	-192.50	0.00

Table 3 (*continued*)

Dose	x_i	y_i	x_iy_i	$(x_i- \bar{X})^2$
0.01	-2.00	40.08	-80.17	0.00
0.01	-2.00	33.33	-66.67	0.00
0.01	-2.00	26.58	-53.16	0.00
0.01	-2.00	26.19	-52.38	0.00
0.01	-2.00	41.67	-83.33	0.00
0.01	-2.00	37.96	-75.93	0.00
0.01	-2.00	35.19	-70.37	0.00
0.01	-2.00	43.52	-87.04	0.00
0.01	-2.00	43.52	-87.04	0.00
0.01	-2.00	45.37	-90.74	0.00
0.01	-2.00	50.00	-100.00	0.00
0.10	-1.00	50.00	-50.00	0.90
0.10	-1.00	36.51	-36.51	0.90
0.10	-1.00	39.55	-39.55	0.90
0.10	-1.00	69.40	-69.40	0.90
0.10	-1.00	68.66	-68.66	0.90
0.10	-1.00	29.11	-29.11	0.90
0.10	-1.00	40.93	-40.93	0.90
0.10	-1.00	28.27	-28.27	0.90
0.10	-1.00	33.33	-33.33	0.90
0.10	-1.00	58.33	-58.33	0.90
0.10	-1.00	42.59	-42.59	0.90
0.10	-1.00	66.67	-66.67	0.90
0.10	-1.00	55.56	-55.56	0.90
0.10	-1.00	59.26	-59.26	0.90
0.10	-1.00	69.44	-69.44	0.90
0.30	-0.52	57.14	-29.71	2.04
0.30	-0.52	-3.97	2.06	2.04
0.30	-0.52	58.21	-30.27	2.04
0.30	-0.52	71.64	-37.25	2.04
0.30	-0.52	67.91	-35.31	2.04
0.30	-0.52	45.15	-23.48	2.04
0.30	-0.52	51.06	-26.55	2.04
0.30	-0.52	29.96	-15.58	2.04
0.30	-0.52	36.91	-19.19	2.04
0.30	-0.52	60.71	-31.57	2.04
0.30	-0.52	51.85	-26.96	2.04
0.30	-0.52	75.93	-39.48	2.04
0.30	-0.52	55.56	-28.89	2.04
0.30	-0.52	62.96	-32.74	2.04
0.30	-0.52	77.78	-40.44	2.04

Legend: Dose (nmol/site); x_i: Log of dose (nmol/site); y_i: (% of MEP); x_iy_i: product $x_i.y_i$; $(x_i-\bar{\boldsymbol{X}})^2$: $(x_i - x_i \text{ averaged})^2$.
- Linear regression summary:
$\sum x = -132.32$; $\sum y = 2787$; $N = 72$; $\bar{X} = -1.84$; $\bar{Y} = 38.72$; $\sum x^2 = 320.64$;
$\sum x.y = -4120$; $N.x.y = -5123$; $\bar{X}^2 = 3.38$

$b = \frac{\sum xiyi - \bar{N}xy}{\Sigma xi^2 - \bar{N}x^2}$;

$a = \bar{y} - \bar{b}x$. thus $b = 12.9$ (slope) and $a = 62.5$ *(intercept)*
- Slope variance $= V(b) = \frac{s^2}{\Sigma(xi-X)2}$. wherein $s^2 = Q/(N\text{-}2)$ and $Q = \sum_{i=1}^{N}(yi-a-bxi)$
V(b) = 4.9
- Assessment if slope differs from 0:
$t_{slope} = b/\{V(b)\}^{1/2}$; $t_{slope} = 5.84$ which exceeds t-tabulated, thus slope differs from zero.
t_{table} (N-2 degrees of freedom; P=0.05; from t-distribution) = 1.96
- DE_{20} calculation: DE20 = (20 – a)/b (in log scale); DE20 = −3.28 or 0.5 pmol/site
- Variance of DE_{20} (V_{DE20}); $= s^2 / b^2 [1/N + (x^1-\dot{x})^2/ S_{xx}]$; $V_{DE20} = 0.09$ (in log scale)

Table 4
Doses used in the dose-response curve for intraplantar combination of SB366791 and Phα1β.

Drug pair	SB366791 (nmol/site)	Phα1β (nmol/site)	Composed drug pair (nmol/site)
1	0.012	0.0006	0.013
2	0.037	0.001	0.038
3	0.11	0.005	0.115
4	0.33	0.016	0.346
5	0.99	0.048	1.038
6	2.97	0.144	3.114

Table 5
Doses used in the dose-response curve for concurrent treatment with SB366791 (i.p.) and Phα1β (i.t.).

Drug pair	SB366791 (nmol/site)	Phα1β (nmol/site)	Composed drug pair (nmol/site)
1	0.022	0.00000048	0.02200048
2	0.066	0.0000014	0.0660014
3	0.2	0.0000043	0.2000043
4	0.60	0.00013	0.60013
5	1.8	0.00039	1.80039
6	5.4	0.00117	5.40117

1.2. Calculation of the proportion of constituents in the mixture

a + b = c. wherein:
a = the quantity (in nmol) of SB366791
b = quantity (nmol) of Phα1β
c = sum (in nmol) of quantities of Phα1β and SB366791 in the mixture

•
The proportion of a and b was fixed and calculated according to the formulae below:

a = A x f
b = (1-f) x B; wherein:
A = DE_{20} of SB366791
B = DE_{20} of Phα1β
f = proportion factor.

The factor f was calculated based on the variances of the DE_{20} values from SB366791 (A) and Phα1β (B) according to the formula:

f = V (B) / V (A) + V (B); wherein:
V (A) = variance of DE_{20} of SB366791 and
V (B) = variance of DE_{20} of Phα1β;

– For combination of intraplantar Phα1β with SB366791. f = 0.38
– For combination of intraplantar SB366791 with intrathecal Phα1β. f = 0.69 (Table 4 and 5).

1.3. Summary of linear regression analyses for the agents administered in combination

1.3.1. Phα1β (i.p.) combined with SB366791 (i.p.)

See Table 6.

Table 6
Dose-effect data of Phα1β (i.p.) combined with SB366791 (i.p.) on capsaicin-induced nociception.

Dose	x_i	y_i	x_iy_i	$(x_i–\bar{X})2$
0.013	-1.92	34.00	-64.79	1.57
0.013	-1.92	24.85	-47.71	1.57
0.013	-1.92	3.93	-7.54	1.57
0.013	-1.92	27.50	-52.81	1.57
0.013	-1.92	-19.89	38.19	1.57
0.013	-1.92	-2.37	4.55	1.57
0.013	-1.92	32.66	-62.72	1.57
0.013	-1.92	-63.64	122.18	1.57
0.013	-1.92	25.00	-48.00	1.57
0.013	-1.92	29.09	-55.85	1.57
0.013	-1.92	-20.00	38.40	1.57
0.013	-1.92	25.68	-49.31	1.57
0.038	-1.42	36.81	-52.27	0.57
0.038	-1.42	43.56	-61.85	0.57
0.038	-1.42	26.38	-37.46	0.57
0.038	-1.42	30.86	-43.82	0.57
0.038	-1.42	29.27	-41.57	0.57
0.038	-1.42	44.01	-62.49	0.57
0.038	-1.42	26.09	-37.05	0.57
0.038	-1.42	39.23	-55.71	0.57
0.038	-1.42	38.14	-54.16	0.57
0.038	-1.42	27.05	-38.40	0.57
0.038	-1.42	20.23	-28.72	0.57
0.038	-1.42	16.82	-23.88	0.57
0.115	-0.93	15.95	-14.83	0.07
0.115	-0.93	46.01	-42.79	0.07
0.115	-0.93	27.61	-25.67	0.07
0.115	-0.93	50.10	-46.59	0.07
0.115	-0.93	44.09	-41.00	0.07
0.115	-0.93	28.09	-26.13	0.07
0.115	-0.93	32.22	-29.96	0.07
0.115	-0.93	46.37	-43.12	0.07
0.115	-0.93	26.09	-24.27	0.07
0.115	-0.93	41.42	-38.52	0.07
0.115	-0.93	37.59	-34.96	0.07
0.115	-0.93	31.82	-29.59	0.07
0.115	-0.93	25.00	-23.25	0.07
0.115	-0.93	16.00	-15.01	0.07
0.115	-0.93	16.82	-15.64	0.07
0.346	-0.46	51.53	-23.71	0.04
0.346	-0.46	52.15	-23.99	0.04
0.346	-0.46	31.90	-14.67	0.04
0.346	-0.46	54.31	-24.98	0.04
0.346	-0.46	51.30	-23.60	0.04
0.346	-0.46	59.12	-27.19	0.04
0.346	-0.46	40.01	-18.40	0.04
0.346	-0.46	33.99	-15.63	0.04
0.346	-0.46	46.90	-21.57	0.04
0.346	-0.46	60.04	-27.62	0.04
0.346	-0.46	74.27	-34.16	0.04
0.346	-0.46	35.91	-16.52	0.04
0.346	-0.46	30.45	-14.01	0.04

Table 6 (*continued*)

Dose	x_i	y_i	x_iy_i	$(x_i–\bar{X})2$
0.346	-0.46	36.59	-16.83	0.04
0.346	-0.46	15.45	-7.11	0.04
1.038	0.02	52.76	0.84	0.47
1.038	0.02	60.12	0.96	0.47
1.038	0.02	53.99	0.86	0.47
1.038	0.02	86.77	1.39	0.47
1.038	0.02	49.50	0.79	0.47
1.038	0.02	63.93	1.02	0.47
1.038	0.02	54.03	0.86	0.47
1.038	0.02	45.78	0.73	0.47
1.038	0.02	49.90	0.80	0.47
1.038	0.02	49.64	0.79	0.47
1.038	0.02	65.51	1.05	0.47
1.038	0.02	59.49	0.95	0.47
1.038	0.02	45.45	0.73	0.47
1.038	0.02	45.45	0.73	0.47
1.038	0.02	16.14	0.26	0.47
1.038	0.02	50.23	0.80	0.47
3.114	0.49	54.60	26.75	1.34
3.114	0.49	63.80	31.26	1.34
3.114	0.49	66.26	32.47	1.34
3.114	0.49	69.94	34.27	1.34
3.114	0.49	61.52	30.15	1.34
3.114	0.49	65.13	31.91	1.34
3.114	0.49	61.10	29.94	1.34
3.114	0.49	58.74	28.78	1.34
3.114	0.49	68.17	33.40	1.34
3.114	0.49	67.70	33.17	1.34
3.114	0.49	68.25	33.44	1.34
3.114	0.49	72.08	35.32	1.34

Legend: Dose (nmol/site); x_i: Log of dose (nmol/site); y_i: (% of MEP); x_iy_i: product $x_i.y_i$; $(x_i–\bar{X})^2$: (x_i –x_i averaged)^2.
- Linear regression summary:
$\sum x = -54.8$; $\sum y = 3260$; $N = 82$; $\bar{X} = 0.66822$; $\bar{Y} = 40$; $\sum x^2 = 87.4664$;
$\sum x.y = -1089.7$; $N.x.y = -2178.55$; $\bar{X}^2 = 0.446517$

$b = \frac{\sum xiyi - \bar{N}xy}{\sum xi^2 - \bar{N}x^2}$;

$a = \bar{y} - \bar{b}x$. thus $b = 21.4$ (slope) and $a = 54.1$ *(intersept)*
- Slope variance $= V(b) = \frac{s^2}{\Sigma(xi-X)2}$. wherein $s^2 = Q/(N\text{-}2)$ and $Q = \sum_{i=1}^{N}(yi-a-bxi)$
V(b) = 4.9
- Assessment if slope differs from 0:
$t_{slope} = b/\{V(b)\}^{1/2}$; $t_{slope} = 9.64$ which exceeds t-table, thus slope differs from zero
t_{table} (N-2 degrees of freedom; P=0.05; from t-distribution) = 1.96
- DE_{20} calculation: DE20 = (20 – a)/b (in log scale); DE20 = –1.59 or 0.025 nmol/site
- Variance of DE_{20} (V_{DE20}); $= s^2 / b^2 [1/N + (x^1-\ddot{x})^2/ S_{xx}]$; $V_{DE20} = 0.016$ (in log scale)

1.3.2. Phα1β (i.t.) combined with SB366791 (i.p.)

See Table 7.

Table 7
Dose-effect data Phα1β (i.t.) and SB366791 (i.p.) on capsaicin-induced nociception.

Dose	x_i	y_i	x_iy_i	$(x_i–\bar{X})2$
0.022	-1.66	2.00	-3.07	1.50
0.022	-1.66	-33.77	56.06	1.50
0.022	-1.66	32.95	-54.70	1.50
0.022	-1.66	-34.79	57.76	1.50
0.022	-1.66	29.24	-48.54	1.50
0.022	-1.66	32.19	-53.43	1.50
0.022	-1.66	49.14	-81.57	1.50
0.022	-1.66	5.42	-9.00	1.50
0.022	-1.66	23.73	-39.39	1.50
0.022	-1.66	37.13	-61.64	1.50
0.022	-1.66	52.16	-86.59	1.50
0.022	-1.66	34.40	-57.10	1.50
0.066	-1.18	15.30	-18.06	0.56
0.066	-1.18	51.72	-61.02	0.56
0.066	-1.18	50.92	-60.09	0.56
0.066	-1.18	25.35	-29.91	0.56
0.066	-1.18	-29.95	35.35	0.56
0.066	-1.18	34.40	-40.59	0.56
0.066	-1.18	39.56	-46.68	0.56
0.066	-1.18	49.14	-57.99	0.56
0.066	-1.18	24.75	-29.20	0.56
0.066	-1.18	32.88	-38.80	0.56
0.066	-1.18	34.40	-40.59	0.56
0.066	-1.18	26.88	-31.72	0.56
0.200	-0.69	27.18	-18.75	0.07
0.200	-0.69	5.01	-3.46	0.07
0.200	-0.69	54.88	-37.87	0.07
0.200	-0.69	14.98	-10.33	0.07
0.200	-0.69	-2.30	1.59	0.07
0.200	-0.69	50.23	-34.66	0.07
0.200	-0.69	52.09	-35.94	0.07
0.200	-0.69	46.93	-32.38	0.07
0.200	-0.69	68.30	-47.13	0.07
0.200	-0.69	31.86	-21.99	0.07
0.200	-0.69	40.00	-27.60	0.07
0.200	-0.69	59.32	-40.93	0.07
0.200	-0.69	35.08	-24.21	0.07
0.200	-0.69	34.00	-23.73	0.07
0.200	-0.69	55.58	-38.35	0.07
0.600	-0.22	62.01	-13.64	0.05
0.600	-0.22	37.47	-8.24	0.05
0.600	-0.22	35.88	-7.89	0.05
0.600	-0.22	70.28	-15.46	0.05
0.600	-0.22	54.38	-11.96	0.05
0.600	-0.22	53.69	-11.81	0.05
0.600	-0.22	54.30	-11.95	0.05
0.600	-0.22	53.56	-11.78	0.05
0.600	-0.22	65.36	-14.38	0.05
0.600	-0.22	41.02	-9.02	0.05
0.600	-0.22	36.95	-8.13	0.05
0.600	-0.22	59.32	-13.05	0.05
0.600	-0.22	52.16	-11.48	0.05
0.600	-0.22	41.23	-9.07	0.05
0.600	-0.22	56.95	-12.53	0.05

Table 7 (*continued*)

Dose	x_i	y_i	x_iy_i	$(x_i–\bar{X})2$
1.800	0.25	81.00	20.25	0.47
1.800	0.25	71.50	17.88	0.47
1.800	0.25	52.51	13.13	0.47
1.800	0.25	71.66	17.91	0.47
1.800	0.25	57.14	14.29	0.47
1.800	0.25	59.22	14.80	0.47
1.800	0.25	74.20	18.55	0.47
1.800	0.25	54.30	13.57	0.47
1.800	0.25	67.57	16.89	0.47
1.800	0.25	52.20	13.05	0.47
1.800	0.25	43.05	10.76	0.47
1.800	0.25	63.39	15.85	0.47
1.800	0.25	44.65	11.16	0.47
1.800	0.25	48.75	12.19	0.47
1.800	0.25	63.78	15.95	0.47
5.400	0.73	77.88	56.85	1.36
5.400	0.73	57.83	42.22	1.36
5.400	0.73	68.89	50.29	1.36
5.400	0.73	76.41	55.78	1.36
5.400	0.73	56.51	41.25	1.36
5.400	0.73	69.78	50.94	1.36
5.400	0.73	65.42	47.76	1.36
5.400	0.73	52.20	38.11	1.36
5.400	0.73	67.46	49.24	1.36
5.400	0.73	57.63	42.07	1.36
5.400	0.73	61.05	44.56	1.36
5.400	0.73	65.15	47.56	1.36

Legend: Dose (nmol/site); x_i: Log of dose (nmol/site); y_i: (% of MEP); x_iy_i: product $x_i.y_i$; $(x_i–\bar{\mathbf{X}})^2$: (x_i –x_i averaged)^2.
- Linear regression summary:
$\sum x$= -35.22; $\sum y$= 3614; N=81; $\bar{X}$= -0.43481; $\bar{Y}$= 45; $\sum x^2$ = 64.9758;
$\sum x.y$= -573.761; N.x.y = -1571.51; $\bar{X}^2$= 0.1890

b= $\frac{\sum xiyi-\bar{N}xy}{\Sigma xi^2-\bar{N}x^2}$;

$a = \bar{y} - \bar{b}x$. thus b = 20.1 (slope) and a = 53.4 *(intersept)*
- Slope variance = $V(b) = \frac{s^2}{\Sigma(xi-X)2}$. wherein s^2 = $Q/(N\text{-}2)$ and Q = $\sum_{i=1}^{N}(yi-a-bxi)$
V(b) = 5.1
- Assessment if slope differs from 0:
t_{slope} = b/{V(b)}$^{1/2}$; t_{slope} = 7.99 which exceeds t-tabulated. Thus, slope differs from zero
t_{table} (N-2 degrees of freedom; P=0.05; from t-distribution) = 1.96
- DE_{20} calculation: DE20 = (20 – a)/b (in log scale); DE20 = -1.66 or 0.022 nmol/site
- Variance of DE_{20} (V_{DE20}); = s^2 / b^2 [1/N + $(x^1–\ddot{x})^2$/ S_{xx}]; V_{DE20} = 0.033 (in log scale)

1.4. Statistical comparisons between experimentally obtained DE_{20} (Z_{mix}) and Theoretical additive DE_{20} (Z_{add})

– ***Calculation of the Z_{add}.***
– Z_{add} = f.A + (1-f). B wherein:

f = the proportion factor (obtained from topic B);
A = DE_{20} of SB366791;
B = DE_{20} of Phα1β.

Table 8
Compilation of the comparison test.

Route of combined agents	Z_{add}(nMol)	Z_{mix} (nMol)	$t_{critical}$	$T_{tabulated}$	Statistical significance
Intraplantar/Intraplanar	0.35	0.025	6.37	1.96	Yes
Intraplantar/Intrathecal	0.34	0.022	5.44	1.96	Yes

– Variance of Z_{add} = f^2. V(A) + $(1\text{-}f)^2$. V(B). wherein

f = proportion factor;
V(A) and V(B) = Variances of the DE_{20} of SB366791 and Phα1β, respectively.

– **Comparison test**
– $t_{critical} = (x\text{-}y)/[(SEx)^2+(SEy)^2]^{1/2}$; wherein:

x = Log of Z_{add}
y = Log of Z_{mix}
$(SEx)^2 = V(Z_{add})$
$(SEy)^2 = V(Z_{mix})$

– $T_{tabulated} = [t_{add}(SEx)_2+t_{mix}(SEy)^2]/[(SEx)^2+(SEy)^2]$; where in:

t_{add} = tabular value of t based on N´-2 degrees of freedom for 95% of significance
t_{mix} = tabular value of t based on N-2 degrees of freedom for 95% of significance
$(SEy)^2$= Variance of Z_{mix}

Interpretation: If $t_{critical} < T_{tabulated}$, then the difference is not significant, which means an additive effect. When $t_{critical} > T_{tabulated}$, Z_{mix} is significantly smaller (95% of confidence) than the Z_{add}, which implies a synergistic effect of combined drugs (Table 8).

2. Experimental design, materials and methods

2.1. Capsaicin-induced nociceptive responses

This test was conducted essentially as described previously [1]. Briefly, individual animals were placed in transparent acrylic square boxes (20 cm per side) immediately after the capsaicin injection (1 nmol/paw i.p.), and nociceptive behaviours were recorded continuously for 300 s. Behaviours were quantified by recording the time spent licking, biting or flinching (nociceptive time) the paw injected with capsaicin. Phα1β (i.t. or i.p), SB366791 (i.p.), combined Phα1β + SB366791 or their respective vehicles were injected 10 min before the capsaicin injection. The initial dose ranges of Phα1β and SB366791 were selected based on previous data [1]. Antinociceptive effects were measured as a percentage of the maximum possible (% MPE) effect according to the formula: % MPE = 100*(A – B / A), where A is the averaged nociceptive time of the vehicle group and B is the nociceptive time of each animal in the treated group (drugs alone or in combination) [2].

2.2. Experimental design and statistical isobolographic analysis

Experimental design and statistical analyses were conducted essentially as previously described [3–5]. Briefly, dose-response curves were first obtained for Phα1β and SB366791 administered alone. Line equations, slope values and respective variances were obtained using linear regression [3]. DE_{20} values and 95% confidence limits were calculated using probit analysis. DE_{20} values (doses that exhibit 20% MPE) were used to assess whether the dose-effect of these drugs alone exhibited a constant potency ratio, which is necessary to perform fixed dose-pair combination of drugs [4].

Drug doses in association studies were determined as a proportion of their DE_{20} values. This proportion was constant and estimated based on a factor derived from the individual variances of the DE_{20} values. This fixed proportion of agents was necessary to assess whether the combination displayed enhanced potency indicative of synergism. Dose-response curves of associated drugs were constructed to obtain the doses that achieved the same effect level (20% MPE) compared to drugs given alone. This experimentally obtained DE_{20} (here called Z_{mix}) was compared to theoretically calculated DE_{20} value for additive interactions (Z_{add}). The criterion for establishing a statistical significance was $P < 0.05$. Graphical assessments of synergy are also presented using isobolographic analyses. Measurement of the interaction index (α) was obtained by dividing experimentally obtained DE_{20} of the drug pair by the theoretical additive DE_{20} of the drug pair. The α interaction index provides a measure of the degree of synergism.

Acknowledgements

We thank Dr. Ronald J. Tallarida (*in memorian*) for the support on the isobolographic experimental design. We also thank for the funding agencies for supporting this work: Fapemig CBB-RED-00006-14, CNPq Universal 456048/2014, FAPEMIG Universal APQ-01553-14, Capes Toxinology 1444/2011, Capes Decit 2865/10, and INCT Medicina Molecular, CNPq 471070-2012. We thank those funds agencies for fellowship support.

Transparency document. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dib.2017.07.059.

References

[1] C.J. Castro-Junior, J. Milano, A.H. Souza, J.F. Silva, F.K. Rigo, G. Dalmolin, M.N. Cordeiro, M. Richardson, A.G. Barros, R. S. Gomez, et al., Ph < alpha > 1 < beta > toxin prevents capsaicin-induced nociceptive behavior and mechanical hypersensitivity without acting on TRPV1 channels, Neuropharmacology 71 (2013) 237–246.
[2] M.R. Palhares, J.F. Silva, M.S. Rezende, D.C. Santos, C.A. Silva-Junior, M.H. Borges, J. Ferreira, M.V. Gomez, C.J. Castro-Junior, Synergistic antinociceptive effect of a calcium channel blocker and a TRPV1 blocker in an acute pain model in mice, Life Sci. (2017), in press.
[3] R.J. Tallarida, Drug synergism and dose-effect data analysis. Chapmann & Hall/CRC 1st. ed, 2000.
[4] R.J. Tallarida, Drug synergism: its detection and applications, J. Pharmacol. Exp. Ther. 298 (2001) 865–872.
[5] R.J. Tallarida, An overview of drug combination analysis with isobolograms, J. Pharmacol. Exp. Ther. 319 (2006) 1–7.