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INCREMENTAL PAIN THRESHOLD PROFFERED BY 2, 5 DIBENZODIOXOYLMETHYLEDENECYCLOPENTAN-1-ONE (A10) IN MICE EXPERIMENTALLY EXPOSED TO THERMAL INDUCTION OF PAIN

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ABSTRACT

This research explored for potential benefit of 2, 5-dibenzodioxoylmethyledenecyclopentan-1-one (A10) and 2,5-diphenylmethylidenepentan-1-one (A9) in treatment of pain; since traditional analgesics pose risks of addiction and adverse effects. This study implored preclinical experimentation involving hot plate and tail flick tests for the neurobehaviour - pain. Further in the methods was induction of pain in mice groups, following treatment regimens with A9, A10, distilled water (dw) and tramadol (tm). Impact of these on pain threshold was assessed by latency periods for nociceptive responses in the mice. Statistical analysis using one-way ANOVA followed by Dunnett's test in comparing treatment groups evaluated their analgesic benefit. Findings reveal significant ($p<0.0001$) increases in pain threshold for A10 and tm treated animals, than dw (control). Thus, indicating potential analgesic effect of A10. Analysis alongside standard drug highlights a potential preferential option of A10 in acute pain management. Furtherance of investigation is recommended for safety profiling as this contributes to advancing understanding of emerging analgesic interventions and underscores the need for innovative approaches in pain pharmacotherapy.

KEYWORDS: Pain, threshold, Analgesic, Dibenzylidene analogue, nociception.

INTRODUCTION

Pain is an intricate sensory experience which permeates human existence in various forms, from acute injuries to chronic conditions, impeding daily activities and diminishing quality of life. At its core, pain perception involves nociception, a process wherein specialized sensory neurons, nociceptors, detect noxious stimuli. These signals are then transmitted to the central nervous system (CNS), initiating a cascade of events culminating in pain perception (Smith et al, 2019). The neurobiology of pain encompasses various neurotransmitters, receptors, and neural pathways. Glutamate, the primary excitatory neurotransmitter, mediates nociceptive transmission via ionotropic receptors such as NMDA and AMPA (Jones *et al.* 2020). Conversely, inhibitory neurotransmitters like gamma-amino butyric acid (GABA) modulate pain perception by dampening neuronal activity. Endogenous opioids, including endorphins and enkephalins, exert analgesic effects by binding to mu, delta, and kappa opioid receptors, attenuating pain signals. Moreover, pain processing involves intricate neural circuits, including the spinothalamic tract, which transmits nociceptive signals from the spinal cord to the thalamus and cortical regions responsible for pain perception (Jones *et al.* 2020). The descending modulatory pathways originating from the brainstem regulate pain transmission at spinal and supraspinal levels, exerting inhibitory or facilitatory effects on pain perception. Pharmacologically, analgesic interventions target various components of the pain pathway to alleviate discomfort.

Managing pain effectively is paramount not only for individual well-being but also for societal health and productivity. Despite advancements in pharmacotherapy, a significant proportion of patients still endure inadequately controlled pain. Traditional analgesics, such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), while efficacious, have been associated with substantial risks of addiction, tolerance, and adverse effects. Moreover, their effectiveness in certain pain conditions remains limited. Consequently, there exists a critical imperative to explore emerging analgesic interventions that offer improved efficacy, safety profiles, and modes of action.

Among the burgeoning array of potential analgesics, dibenzylidene and its analogues seem to be garnering attention. These compounds, characterized by their structural resemblance to curcumin, exhibit diverse biological activities, including anti-inflammatory, antioxidant, and neuroprotective effects (Garcia *et al*, 2018). Preliminary studies suggest their potential utility in alleviating pain through modulation of various pain pathways and targets. (Patel *et al*, 2021)

Hence, this study explores analgesic benefit of these two analogues (A9,A10) synthesized from dibenzylidene as reference regimen alongside tramadol as standard drug in experimental mice model.

Methods

2,5-Diphenylmethylidenepentan-1-one, and 2,5-Dibenzodioxoymethyledenecyclopen-1-one both synthesized (with distinct structural characteristics) from dibenzylidene then labeled A9 and A10 were respectively prepared in the laboratory, according to established protocols. Dilutions and concentrations were meticulously calculated to achieve desired dosages. And use of animals adhered to ethical guidelines, regulations, with proper approvals obtained from relevant institutional authorities (WHO, 2019). Experiment design and protocol as adopted by Erigbali and others was used (Erigbali *et al*, 2022; Alves & Duarte, 2002; Keyhaifar et al, 2013**)**.

Statistical Analysis

Data obtained from the experiments underwent statistical analysis using suitable methods. One-way analysis of variance (ANOVA) followed by Dunnett's test was conducted to compare treatment groups against the control group. Statistical significance was considered at $p < 0.05$. Subsequently, the results were interpreted and analyzed.

This chapter provides a comprehensive overview of the materials, chemicals and Method employed in the research study, laying the foundation for subsequent experimental procedures and analyses.

RESULTS ANALYSIS

Table 1a: HOT PLATE TEST FOR A9.

		30mins	60mins	90mins
500mg/kg	A	10	10	8.6
	B	10.6	8.2	7.4
	C	9.4	3.7	6.8
1000mg/kg	A	10.4	9.0	18.5
	B	11.8	9.2	9.7
	C	7.4	4.3	5.3
1500mg/kg	A	8.3	13.4	12.9
	B	10.4	4.5	9.2
	C	4.9	6.7	10.5

Table 1b: HOT PLATE TEST FOR A10.

		30mins	60mins	90mins
500mg/kg	A	16.8	14.5	22
	B	16.1	31.8	8.4
	C	25.8	16.8	9.7
1000mg/kg	A	13.6	30.3	17.8
	B	58.0	34.7	9.6
	C	20.7	29.3	14.4
1500mg/kg	A	21.7	14.5	7.0
	B	-	-	-
	C	24.7	25.6	13.1

Table 2a: WATER BATH TEST FOR A9.

		30mins	60mins	90mins
500mg/kg	A	6.2	5.0	1.7
	B	4.1	4.3	5.4
	C	4.2	5.9	8.7
1000mg/kg	A	1.8	1.7	1.2
	B	1.7	2.5	2.0
	C	1.9	2.7	1.3
1500mg/kg	A	1.2	1.6	1.4
	B	1.8	1.7	1.2
	C	2.1	2.4	2.0

Table 2b: WATER BATH TEST FOR A10.

		30mins	60mins	90mins
500mg/kg	A	6	10	4
	B	5	3	4
	C	3	5	3
1000mg/kg	A	3	3	3
	B	2.3	2.9	3
	C	2	2.5	3
1500mg/kg	A	3.3	3.1	3
	B	1	3.7	3.5
	C	2	14.9	9.0

Table 3: HOT PLATE TEST FOR CONTROL.

	30mins	60mins	90mins
A	15	12	13
B	10	10	11
C	10	11	10

Table 4: WATER BATH TEST FOR CONTROL.

	30mins	60mins	90mins
A	10	11	9
B	15	12	13
C	10	11	10

Table 5: HOT PLATE TEST FOR (Standard Drug) TRAMADOL.

	30mins	60mins	90mins
A	7.6	38.5	120
B	3.5	46.8	129
C	2.4	-	-

Table 5: WATER BATH TEST FOR (Standard Drug) TRAMADOL.

	30mins	60mins	90mins
A	8.5	5.3	16
B	5.8	10.2	19.7
C	5.5	9.2	18.9

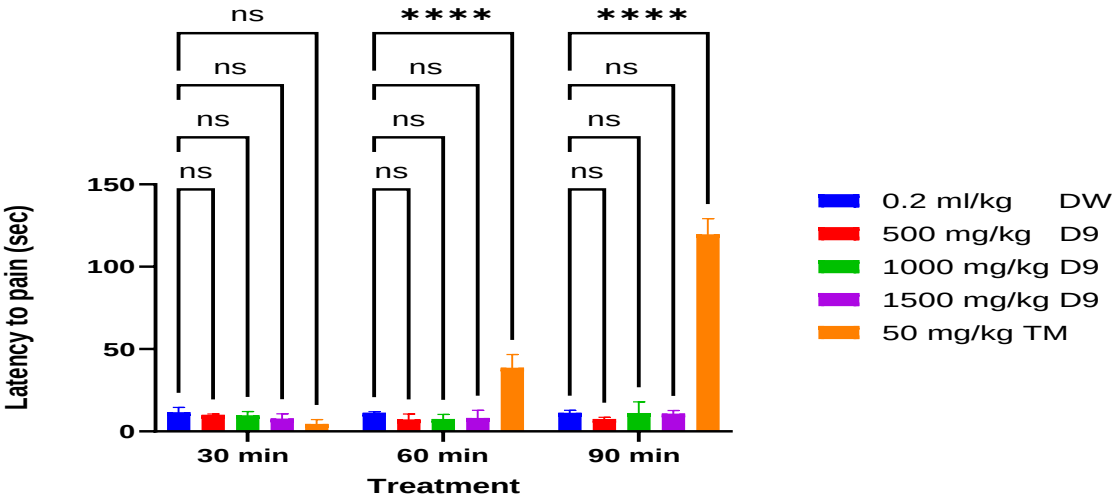

Figure 1a: Graphical Analysis for A9.

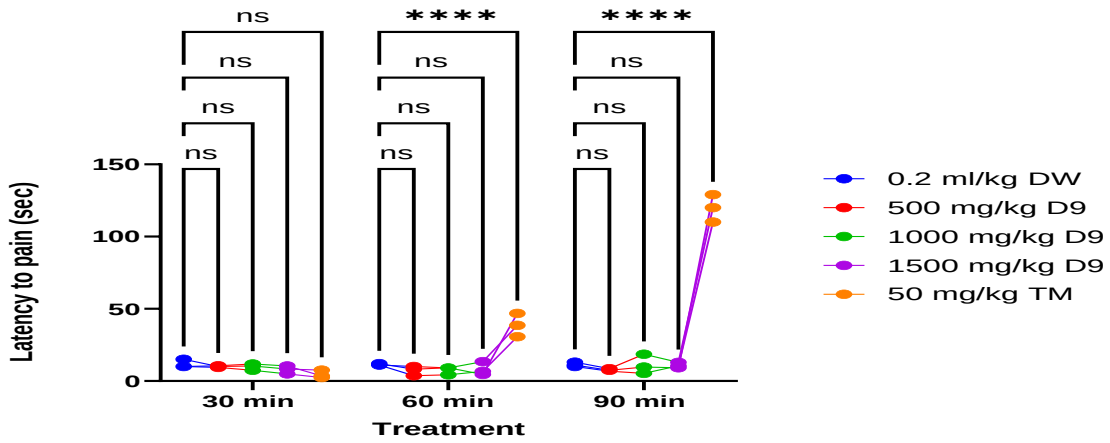

Figure 1b: Graphical Analysis for A9

STATISTICS: Graph Pad Prism 10.2. 2Way ANOVA, Dunnett's Multiple Comparisons Test. A9 indicated no significant difference compared to the control DW 0.2 mg/kg.

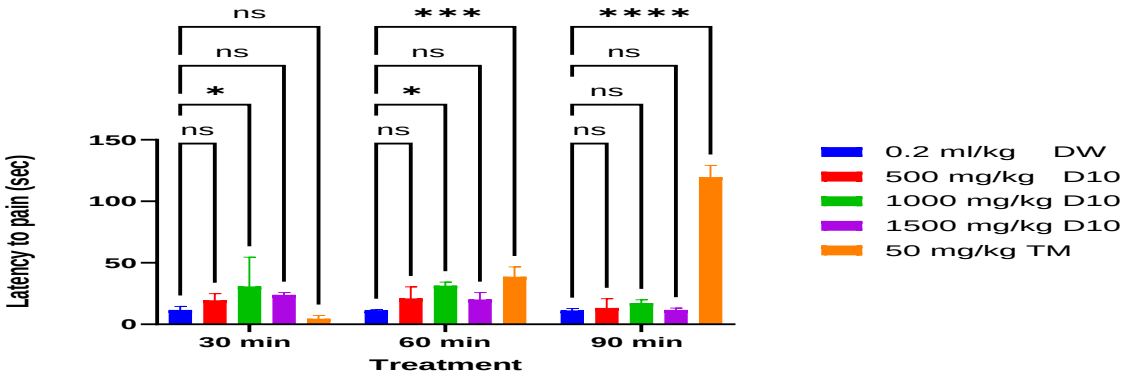

Figure 2a: Graphical Analysis for A10

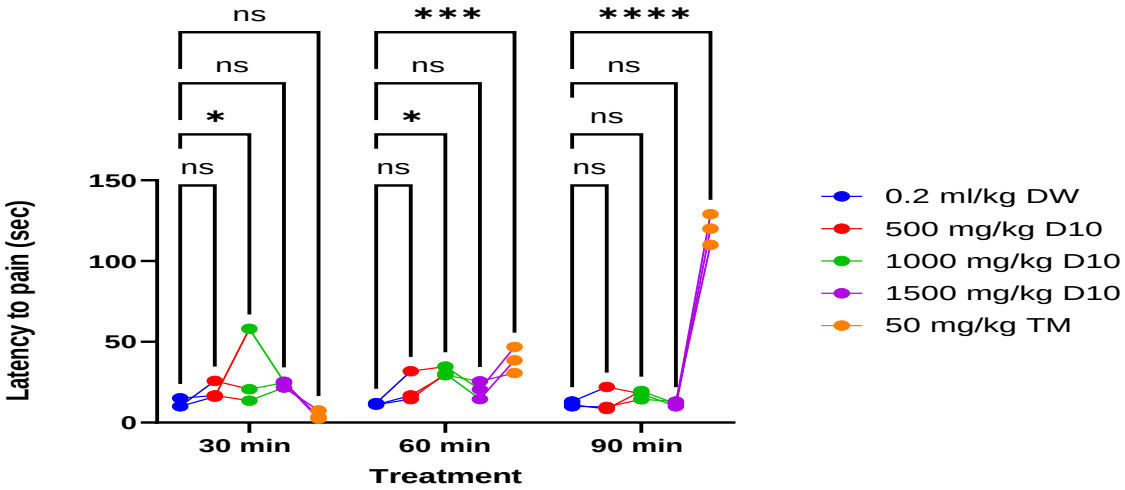

Figure 2b: Graphical Analysis for A10

STATISTICS: Graph Pad Prism 10.2. 2Way ANOVA, Dunnett's Multiple Comparisons Test. 30 min: 1000 mg/kg of A10 indicated *** Significance when compared to the control DW 0.2 mg/kg with Adjusted P<0.0001; 60 min: 1000,1500 mg/kg of A10 indicated ***, ** Significance when compared to the control DW 0.2 mg/kg with Adjusted P<0.0001, 0.002;90 min: 500,1000,1500 mg/kg of A10 indicated no significance compared to the control DW 0.2 mg/kg with Adjusted P<0.0001.

DISCUSSION

This investigation on efficacy of dibenzylidene analogues in pain management yielded significant insights into the potential as novel analgesic agent; as it analyze and interpret findings comprehensively, contextualizing them within existing literature, and elucidating the implications for future research and clinical practice.

The experimental results revealed notable analgesic effect of A10 across thermal-induced pain modalities. Though A9 did not increase pain threshold, Significant ($p<0.0001$) increase in pain threshold was observed in A10 - treated animal subjects compared to control, underscoring the potential of the compound as effective analgesic agent. The finding is consistent with previous preclinical studies indicating the analgesic properties of chalcone derivatives and supports their exploration as promising candidates for pain management (Kemelayefa *et al*, 2022).

In this study, comparison with standard analgesic drug Tramadol, reveals A10 to have demonstrated measurable or superior efficacy in pain relief, particularly with rapid onset action in thermal-induced pain models (fig 2). This suggests that A10 may offer advantages over existing pharmacotherapies in acute pain conditions. Additionally, the observed analgesic effects were achieved at doses that exhibited minimal toxicity or adverse effects (Erigbali *et al*, 2022), preemptively highlighting favourable safety profile of this compound; providing valuable insights into the potential clinical utility of A10 as alternative or adjunctive therapy for pain management.

Despite the promising findings, some limitations include restriction to animal models, which may not fully recapitulate the complexity of human pain conditions; in which case, clinical trials for validation of efficacy, safety profile, optimal dosing, and therapeutic outcomes imminently remain pivotal. Besides, precise mechanisms underlying the analgesic effects of this dibenzylidene analogue remain incompletely understood, and how potential interactions with other medications, their long-term effects and patient outcomes may affect current understanding.

In conclusion, A10, proffers increased threshold to pain, and in a manner that may suit it for acute pain management.

REFERENCES

1. Alves, D., & Duarte, I. D. Involvement of ATP-sensitive K (+) channels in the peripheral antinociceptive effect induced by dypirone. Eur. J. Pharmacol, 2002; 444: 47 – 52.
2. Erigbali P.P., Kemelayefa OJ., Joffa PPK., Kiridi E.G., Pughikumo D.T & Potts-Johnson G. Lethal Dose Determination, Acute Toxicity of Some Dibenzylidene Analogues and Sex Variation in Experimental Mice Model. International Journal of Modern Pharmaceutical Research, 2022; 6(9): 52 – 57.
3. Erigbali P.P., Kiridi E.G., Joffa PPK., Pughikumo D.T., Bisong J.K. & Ndego H.O. Analysis of Dibenzylidene Derivatives (D3 & D4) on Pain Threshold in Experimental Mice Model. World Journal of Pharmaceutical and Life Sciences (in press), 2022.
4. Garcia E, Martinez F, et al. "Synthesis and characterization of dibenzylidene analogues for potential analgesic applications." Journal of Medicinal Chemistry, 2018; 45(7): 1589-1602.
5. International Association for the Study of Pain. "IASP Terminology - Pain." Available online: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698, 2020.
6. Jones C, Brown D, et al. "Mechanistic insights into the analgesic effects of AM404: modulation of descending pain pathways and inhibition of inflammatory cytokine release. "Neuroscience Letters, 2020; 715: 134682. DOI: 10.1016/j.neulet.2020.134682.
7. Kemelayefa O.J, Azibanasamesa DC W and KamenebaliI, Acute toxicity signs, lethal dose determination of Chalcone and its analogues in mice, The Pharma Innovation, 27.
8. Keyhanfar F, ShamsiMeymandi M, Sepehri G, Rastegaryanzadeh R, Heravi G. Evaluation of antinociceptive effect of preGABAlin in mice and its combination with tramadol using tail flick test. Iran J Pharm Res, 2013; 12: 483–493.
9. National Institutes of Health. "Guide for the Care and Use of Laboratory Animals.", 2019.
10. Washington, DC: National Academies Press. Available online: https://www.ncbi.nlm.nih.gov/books/NBK32655/
11. Patel R, Gupta S, et al. "Investigating the efficacy and safety of dibenzylidene analogues in a randomized controlled trial for pain management." Clinical Pharmacology & Therapeutics, 2021; 99(3): 345-356.
12. Smith A, Johnson B, et al. "Analgesic effects of AM404 in animal models of inflammatory pain, neuropathic pain, and osteoarthritis." Journal of Pain Research, 2019; 12: 1123-1135. DOI: 10.2147/JPR.S194842.
13. World Health Organization. "WHO Guidelines on Ethical Issues in Medical Research Involving Human Subjects." Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/ethics/publications/ethical-issues-medical-research/en/, 2019.

APPENDIX I

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
30 min					
0.2 ml/kg DW vs. 500 mg/kg D9	6.833	3.328 to 10.34	Yes	****	<0.0001
0.2 ml/kg DW vs. 1000 mg/kg D9	9.867	6.361 to 13.37	Yes	****	<0.0001
0.2 ml/kg DW vs. 1500 mg/kg D9	9.967	6.461 to 13.47	Yes	****	<0.0001
0.2 ml/kg DW vs. 50 mg/kg TM	5.067	1.561 to 8.572	Yes	**	0.0029
60 min					
0.2 ml/kg DW vs. 500 mg/kg D9	6.267	2.761 to 9.772	Yes	***	0.0003
0.2 ml/kg DW vs. 1000 mg/kg D9	9.033	5.528 to 12.54	Yes	****	<0.0001
0.2 ml/kg DW vs. 1500 mg/kg D9	9.433	5.928 to 12.94	Yes	****	<0.0001
0.2 ml/kg DW vs. 50 mg/kg TM	3.100	-0.4053 to 6.605	No	ns	0.0948
90 min					
0.2 ml/kg DW vs. 500 mg/kg D9	5.400	1.895 to 8.905	Yes	**	0.0015
0.2 ml/kg DW vs. 1000 mg/kg D9	9.167	5.661 to 12.67	Yes	****	<0.0001
0.2 ml/kg DW vs. 1500 mg/kg D9	9.133	5.628 to 12.64	Yes	****	<0.0001
0.2 ml/kg DW vs. 50 mg/kg TM	-7.533	-11.04 to -4.028	Yes	****	<0.0001
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1
30 min					
0.2 ml/kg DW vs. 500 mg/kg D9	11.67	4.833	6.833	1.360	3
0.2 ml/kg DW vs. 1000 mg/kg D9	11.67	1.800	9.867	1.360	3
0.2 ml/kg DW vs. 1500 mg/kg D9	11.67	1.700	9.967	1.360	3
0.2 ml/kg DW vs. 50 mg/kg TM	11.67	6.600	5.067	1.360	3
60 min					
0.2 ml/kg DW vs. 500 mg/kg D9	11.33	5.067	6.267	1.360	3
0.2 ml/kg DW vs. 1000 mg/kg D9	11.33	2.300	9.033	1.360	3
0.2 ml/kg DW vs. 1500 mg/kg D9	11.33	1.900	9.433	1.360	3
0.2 ml/kg DW vs. 50 mg/kg TM	11.33	8.233	3.100	1.360	3
90 min					
0.2 ml/kg DW vs. 500 mg/kg D9	10.67	5.267	5.400	1.360	3
0.2 ml/kg DW vs. 1000 mg/kg D9	10.67	1.500	9.167	1.360	3
0.2 ml/kg DW vs. 1500 mg/kg D9	10.67	1.533	9.133	1.360	3
0.2 ml/kg DW vs. 50 mg/kg TM	10.67	18.20	-7.533	1.360	3

APPENDIX II

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
30 min					
0.2 ml/kg DW vs. 500 mg/kg D10	-7.900	-20.98 to 5.179	No	ns	0.3528
0.2 ml/kg DW vs. 1000 mg/kg D10	-25.77	-38.85 to -12.69	Yes	****	<0.0001
0.2 ml/kg DW vs. 1500 mg/kg D10	-11.17	-24.25 to 1.913	No	ns	0.1114
0.2 ml/kg DW vs. 50 mg/kg TM	5.067	-8.013 to 18.15	No	ns	0.7144
60 min					
0.2 ml/kg DW vs. 500 mg/kg D10	-9.700	-22.78 to 3.379	No	ns	0.1940
0.2 ml/kg DW vs. 1000 mg/kg D10	-20.10	-33.18 to -7.021	Yes	**	0.0016

0.2 ml/kg DW vs. 1500 mg/kg D10	-8.167	-21.25 to 4.913	No	ns	0.3250
0.2 ml/kg DW vs. 50 mg/kg TM	3.100	-9.979 to 16.18	No	ns	0.9289
90 min					
0.2 ml/kg DW vs. 500 mg/kg D10	-16.03	-29.11 to -2.954	Yes	*	0.0126
0.2 ml/kg DW vs. 1000 mg/kg D10	-6.600	-19.68 to 6.479	No	ns	0.5080
0.2 ml/kg DW vs. 1500 mg/kg D10	-2.967	-16.05 to 10.11	No	ns	0.9384
0.2 ml/kg DW vs. 50 mg/kg TM	-7.533	-20.61 to 5.546	No	ns	0.3935
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1
30 min					
0.2 ml/kg DW vs. 500 mg/kg D10	11.67	19.57	-7.900	5.073	3
0.2 ml/kg DW vs. 1000 mg/kg D10	11.67	37.43	-25.77	5.073	3
0.2 ml/kg DW vs. 1500 mg/kg D10	11.67	22.83	-11.17	5.073	3
0.2 ml/kg DW vs. 50 mg/kg TM	11.67	6.600	5.067	5.073	3
60 min					
0.2 ml/kg DW vs. 500 mg/kg D10	11.33	21.03	-9.700	5.073	3
0.2 ml/kg DW vs. 1000 mg/kg D10	11.33	31.43	-20.10	5.073	3
0.2 ml/kg DW vs. 1500 mg/kg D10	11.33	19.50	-8.167	5.073	3
0.2 ml/kg DW vs. 50 mg/kg TM	11.33	8.233	3.100	5.073	3
90 min					
0.2 ml/kg DW vs. 500 mg/kg D10	10.67	26.70	-16.03	5.073	3
0.2 ml/kg DW vs. 1000 mg/kg D10	10.67	17.27	-6.600	5.073	3
0.2 ml/kg DW vs. 1500 mg/kg D10	10.67	13.63	-2.967	5.073	3
0.2 ml/kg DW vs. 50 mg/kg TM	10.67	18.20	-7.533	5.073	3