Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(12):201-204
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

A comparative analyses effects of dexmedetomidine and etomidate on motor coordination and analgesia in rats

Bilge Ozcan[1] and Hülagü Barışkaner[2]

[1]Department of Pharmacology, Karabuk Universty, Karabuk, Turkey
[2]Department of Pharmacology, Selcuk Universty, Konya, Turkey

---

ABSTRACT

Dexmedetomine selective alfa-2 adrenoreceptor agonist is nonnarcotic analgesic, hypnotic and sedative imidazole derivative agent. Etomidate is short acting hypnotic imidazole derivative anesthesic agent. In this study, we aimed to compare the analgesic and motor coordination effects of etomidate and dexmedetomidine in rats. In our study Wistar rats were used. The animals (n = 7) were randomly seperated 7 equal groups; saline group, etomidate group (2,5 mg/kg, 5 mg/kg, 10 mg/kg) and dexmedetomidine group (12,5 µg/kg, 30 µg/kg, 40 µg/kg). Pain measurement tests (von Frey test) and motor coordination (Rotarod) tests of 0th, 15th, 30th and 60th minutes were separately performed for each animal and datas were recorded. 120th minute added for dexmedetomidene and saline group. In von Frey tests etomidate's all doses were found statistically time-dependent significant differences to 0th minute (p<0,05). In the rotarod test 5 mg/kg and 10 mg/kg doses of etomidate were showed sedation at 15th and 30th minutes (p<0,05). In von Frey test dexmedetomidine was found at 15th, 30th and 60th minutes time-dependent significant differences to 0th minute (p<0,05). Also 30 µg/kg and 40 µg/kg doses were showed analgesic effects at 120th minute (p<0,05). Dexmedetomidine was found time and dose-dependent sedative effect in the rotarod test (p<0,05). In our study etomidate and dexmedetomidine were showed effective analgesic and sedative effects on rat models of mechanic pain and rotarod test. These two agents exerted time-dependent analgesic and sedative effects. In von Frey test at 60th minutes, the latency time of the dexmedetomidine higher dose was longer than that etomidate's higher dose. In rotarod test etomidate's higher dose was showed a significant difference at 15th minutes compared dexmedetomidine. However dexmedetomidine's 30 µg/kg dose was showed a significant difference at 30th minute compared to etomidate.

Key words: Analgesia, Dexmedetomidine, Etomidate, Rotarod

INTRODUCTİON

Etomidate, a short acting potent hypnotic, anesthesic agent (1). Carboxylated imidazole etomidate shows similarities to specific α2 agonists belonging to the class of imidazole compounds such as dexmedetomidine. Both etomidate and α2 agonist dexmetetomidine induce sedation/hypnosis with minimal respiratory depression, providing beneficial clinical profile (2,3,4). Dexmedetomine selective α2 agonist is nonnarcotic analgesic, hypnotic and sedative imidazole derivative agent (5,6).

There is no study on comparative the effects of these two drugs's motor performance and analgesic efficacy. Therefore, in this study, we aimed to compare the sedative effects by conducting rotarod test and analgesic by conducting vonFrey test.

MATERIALS AND METHODS

This study was approved by the Selcuk University of Pharmacology Department, Konya, Turkey (acceptance no: 14202011).

Animals and laboratory

Fouty-nine male Sprague-Dawley albino rats (age 10–12 weeks; weight, 250–350 g) were obtained from theKONUDAM (Necmettin Erbakan Universty KONUDAM Deneysel Tıp Uygulama ve Araştırma Merkezi) and placedin a temperature- and humidity-controlled room (21 C;60% [-+5%] humidity) with a 12-hour light:dark cycle. Food and water were provided ad libitum, except during the test periods. The rats were randomly divided into 7 groups (n=7 per group) on the basis of the treatment received: 0.9% sodium chloride saline (control), etomidate and dexmedetomidine.

Drug application

The dosage scheme was chosen according to that used in previously reported related successful studies (7-10). Rats were allocated into 7 groups randomly. Each group received intraperitoneally normal saline (0.9% NaCl) (n = 7), dexmedetomidine (Precedex IV Flacon 200 Mcg 2 ml, Abbott.) at 12,5 µg/kg, 30 µg/kg, 40 µg/kg(n = 7 per each group) and etomidate (Hypnomidate 2 mg/ml 10 ml ampul, Janssen-Cilag) 2,5 mg/kg, 5 mg/kg, 10 mg/kg (n = 7 per each group).

Experimental procedures in the rotarod

Motor incoordination andsedation effects was measured with a rotarod test.Rota-Rod system (Ugo Basile, Italy) was used at a rotating speed of 16 r.p.m.(6). Rats were selected that could remain on the rod for 2 successive trials of 45 s periods each for drug testing. Cut-off time was 300 seconds. Performance was measured 0^{th}, 15^{th}, 30^{th} and 60^{th} minutes after the injection of saline, dexmedetomidine and etomidate.120^{th} minute also added for dexmedetomidine and saline group.

Experimental procedures in the vonFrey test

The hind paw withdrawal threshold was determined using von Frey hairs. Pain measurement tests (von Frey test) of 0^{th}, 15^{th}, 30^{th} and 60^{th} minutes were separately performed for each animal and datas were recorded. 120^{th} minute added for dexmedetomidene and saline group.

Statistical analysis

Data were analyzed using the SPSS software program for Windows, version 21.0. One-way (tek yönlü) Anova test, Post Hoc Tukey HSD test, Paired-Samples T test, Independent Samples T method of statistical analysis was used.A value of pb 0.05 was considered to be statistically significant.

RESULTS

VonFrey Test Results:

Table I.Time-related response of Vonfrey mechanical threshold results (gr). Data are presented as mean [SD]

Time (min)	Control	E2,5mg/kg	E5mg/kg	E10 mg/kg	D12,5µg/kg	D30µg/kg	D40µg/kg
0.	467,1[110,8]	278,1[55,9]	220,4[93,9]	261[98]	324,4[137,1]	245,4[59,1]	216,8[70,4]
15.	401[169,9]	829,7[76,6]	767,9[65,9]	930,28[180,4]	674 [179,8]	556,4[394,6]	573,1[184,1]
30.	370,5[34,2]	639,4[69,4]	680[144,3]	850,71[161,7]	645,4[121,4]	626,1[344,9]	680,8[154]
60.	404,5[121,7]	444 [123,6]	400,5[112,9]	549[157,7]	506,1[136]	546,2[124,3]	612,5[80,1]
120.	318[56,4]				329,1[69,1]	495,7[133,2]	507,8[147,8]

E=Etomidate, D=Dexmedetomidine

In von Frey tests compared with the control groupetomidate's all doses were found statistically time-dependent significant differences to 0^{th} minute ($p<0,05$). Compared etomidate groups with each other, at 15^{th},10 mg/kg dose show significant differences to 5 mg/kg dose ($p<0,05$) (Table I). Therefore at 30^{th},10 mg/kg dose show significant differences to 2,5 mg/kg dose ($p<0,05$)(Table I).

Compared with the control group, dexmedetomidine was found at 15^{th}, 30^{th} and 60^{th} minutes time-dependent significant differences to 0^{th} minute ($p<0,05$)(Table I). But at 120^{th} minute only30 and 40 µg/kg doses were showed analgesic effects($p<0,05$)(Table I). Compared dexmedetomidine groups with each other at 120^{th} min, 30 and 40 µg/kg doseswere showedsignificant differences to12,5 µg/kg doses ($p<0,05$)(Table I).

Compared dexmedetomidine with etomidate,only at 60th minutes, the latency time of the dexmedetomidine higher dose (40 µg/kg) was longer than that etomidate's higher dose10 mg/kg (p<0,05)(Table I).

ROTAROD TEST RESULTS

Table II.Time-related response of Rotarod results (sec). Data are presented as mean [SD]

Time min	Control	E2,5mg/kg	E5mg/kg	E10mg/kg	D12,5µg/kg	D30µg/kg	D40µg/kg
0.	97,4[38,8]	112,8[8,8]	117,4[6,8]	120[1,1]	109[20,12]	110,1[12,5]	120[2,1]
15.	107,3 [25]	101,5[20,9]	53,1[16,9]	0,14[0,4]	72,7[45,5]	39,14[17,4]	21,4[8,4]
30.	110,3 [16,7]	100,8[17,6]	86,1[11,9]	7,71[18,6]	83,1[39,4]	41[24,8]	24,1 [23,2]
60.	111,8[13,9]	116,1[4,56]	110,3 [12,6]	88,4[36,5]	111,5[15,6]	78,1[37,3]	37,2[29,4]
120.	99,8[25,1]				106,7[22,7]	100[22,5]	95,4[25,4]

E=Etomidate, D=Dexmedetomidine

In the rotarod test compared with the control group,etomidate's 5 mg/kg and 10 mg/kg doses were showed sedation at 15th and 30th minutes (p<0,05)(Table II).

Compared with the control group,dexmedetomidine's all doses was found time and dose-dependent sedative effect in the rotarod test (p<0,05)(Table II).

Compared with dexmedetomidine, etomidate's higher dose was showed a significant difference at 15th minutes compared dexmedetomidine higher dose (p<0,05)(Table II). However dexmedetomidine's median dose was showed a significant difference at 30th minute compared to etomidate median dose (p<0,05)(Table II).

DISCUSSION

The main finding of our study is that sedative/hypnotic etomidate shows analgesic effects on mechanical stimulation, also exerted a faster onset recovery of motor coordination performance, dexmedetomidine provided longer analgesic efficacy and motor blockades than etomidate

Carboxylated imidazole etomidate, whichpositive allosteric modulators of $GABA_A$receptor, has showed prolonged the duration of GABAergic inhibitory postsynaptic currents in dissociated rat dorsal horn neurons. At spinal level etomidate-induced changes could contribute to analgesia and general anesthesia(11). Invivo it has been also shown intravenous etomidate depressed dorsal horn neuronal responses to noxious heat, measurement was performed onrats which placed microelectrode in the dorsal horn. This depression was maximal at 0.5 mg/kg. Increasing doses did not cause larger peak depression, butcauses more longlasting depressant effect (12). In compliance withthese studiesetomidate time dependent antinociceptive activity is shown in our experiments. As the analgesic effect begins at selected lowest dose (2.5 mg / kg), increasing doses (5 - 10 mg / kg) is ongoing but did not cause larger peak effect. In our study etomidate has been shown to have an analgesic effect, therefore further studies also need to show this effect in humans.Etomidate widely used for its sedative and hypnotic effects (13).Etomidate-induced sedation was assessed in rodents by rotarod performance test.In mice intraperitoneal given etomidate at dose of 5 mg/kg didn't showed sedative effect, butit was evident at 10 mg/kg dose. (14). In our study, in rats etomidate-induced sedative effect start at 5 mg/kg dose and continue increasing dose. Possibly this difference could be caused from the type of animal.

α2 agonist dexmedetomidine dose-dependent analgesia was shown in acute and chronic pain models (15,16). In tail flick test dexmedetomidine analgesic effects was shown at lowest dose of 12.5 µg/kg, also this effect started at 40th min last up to 120th min. (17). In our study, we demonstrated increased efficacy with increasing doses of analgesic effect up to 120 min.

Guneliat al was showed dexmedetomidine analgesic effect was started at ip doses of 5, 10 and 20µg/kg in hot palte and tail flick test, although sedation was determined at ip doses of 30 and 40 µg/kg in rotarod test(18). In our study, 30 and 40 µg/kg doses was observed sedation starts at 15th min up to 120th min, also 12.5 mg / kg was found in only 15th min short-term sedation.In our study, increasing doses of dexmedetomidine sedative effects it has been shown to be prolonged.

CONCLUSION

Therefore, the long-term analgesic effects of dexmedetomidine could be clinically useful for sedation. However, the recovery time from motor coordination impairment wasmore rapid in the etomidate group than in the

dexmedetomidine group. Therefore etomidate analgesic effects hasn't been showed in human, further studies are needed to evaluate the potential of etomidate for analgesia in clinical studies.

REFERENCES

[1] Doenicke A, Kugler J, Penzel G, Laub M, Kalmar L, Killian J,Bezecny A. *Anaesthesist* **1973**;22:357– 66
[2] Khan ZP, Ferguson CN, Jones RM. *Anaesthesia* **1999**;54:146 – 65
[3] Maze M, Tranquilli W. *Anesthesiology* **1991**;74:581– 605
[4] Paris A, Hein L, Brede M, Brand PA, Scholz J, Tonner PH. *Anesth Analg*. **2007** Dec;105(6):1644-9.
[5] Bhana N, Goa KL, McClellan KJ.. *Drugs*. **2000**;59:263–268.
[6] Aydogan MS, Parlakpinar H, Ali Erdogan M, Yucel A, Ucar M, Sağır M, Colak C. *Curr Ther Res Clin Exp*. **2013** Dec;75:22-6. doi: 10.1016/j.curtheres.**2013**.05.003.
[7] Guneli E, Yavasoglu UK, Apaydin S, Uyar M, Uyar M. *Biochemistry and Behavior*. **2007**; 88, 9–17.
[8] Karadas B, Kaya T, Gulturk S, Parlak A, Gursoy S, Cetin A, Bagcivan I. *European Journal of Pharmacology*. **2007**; 556, 62–68.
[9] Ergün Y, Öksüz H, Atli Y, Kılınc M, Darendeli S. *Journal of Surgical Research*. **2010**; 159,e1–e10.
[10] Duysens J, Inoue M, Van Luijtelaar EL, Dırksen R. *Int J Neurosrience*. **1991**; Vol. 57. pp. 213-217.
[11] Zhang ZX, Hui L, Xian-Ping D, Jin L, Tian-Le X. *Brain Research* **2002**;953, 93–100.
[12] Mitsuyo T, Joseph F. Antognini, MD, Earl C. *Anesth Analg*. **2006**;102:1169–73.
[13] Pinto RF, Bhimani M, Milne WK, Nicholson K. *Can J Rural Med*. **2013**;Fall;18(4):130-6.
[14] Paris A, Philipp M, Tonner PH, Steinfath M, Lohse M, Scholz J, Hein L. *Anesthesiology*. **2003**;Oct;99(4):889-95.
[15] Farghaly HS, Abd-Ellatief RB, Moftah MZ, Mostafa MG, Khedr EM, Kotb HI. *Pain Physician*. **2014** Mar-Apr;17(2):187-95.
[16] Kabalak A, Ekmekçioğlu E, Ceylan A, Kahveci K. *Hippokratia*. **2013** Oct;17(4):326-31.
[17] Karadas B, Kaya T, Gulturk S, Parlak A, Gursoy S, Cetin A, Bagcivan I. *European Journal of Pharmacology*. **2007**; 556, 62–68.
[18] Guneli E, Yavasoglu UK, Apaydin S, Uyar M, Uyar M. *Biochemistry and Behavior*. **2007**; 88, 9–17.