Effects of Intracavernosal Calcium Channel Blockers in Dogs

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✔ Düz kas gevşetici ajanların intrakavernöz enjeksiyonu penil ereksiyon oluşturabilmektedir. Bu deneysel çalışmada, köpeklerde intrakavernöz olarak enjekte edilen kalsiyum kanal blokerlerinin (KKB) etkilerini papaverin ile karşılaştırdık ve klinik uygulanabilirliklerini araştırdık.
Her biri değişik seanslarda olmak üzere,10 erişkin erkek köpeğe intrakavernöz olarak 30 mg papaverin, 10 mg nifedipin, 10 mg nitrendipin ve 2.5 mg verapamil verildi. İntrakavernöz basınç, sistemik arteriyel basınç ve kalp hızı değerleri intrakavernöz enjeksiyonlardan itibaren 45 dakika süreyle izlendi. İstatistiksel değerlendirme "paired student-t" testi ile yapıldı.
Papaverin 10 köpeğin hepsinde tam ereksiyon oluşturdu. Nifedipin 10 köpekten 4 ünde, nitrendipin 5 inde, verapamil ise 6 sında tam ereksiyon oluşturdu. Nifedipin ve nitrendipin önemli kan basıncı düşmelerine ve kalp hızı artışlarına neden oldular.
Sonuç olarak, intrakavernöz KKB lerinin etkilerinin papaverinden üstün olmadığı görüldü. Nifedipin ve nitrendipinin intrakavernöz enjeksiyon için önerilemeyeceği ancak, intrakavernöz farmakoterapötik kombinasyonlarında verapamile yer verebileceği kanısına varıldı.

Anahtar Kelimeler: Penil ereksiyon, intrakavernöz enjeksiyon, nifedipin, nitrendipin, verapamil.

✔ Intracavernous injection of smooth muscle relaxing agents can induce penile erection. In this experimental study, we compared the effects of intracavernosally injected calcium channel blockers (CCBs) and papaverine in dogs, and investigated their clinical applicabilities.
We administered 30 mg papaverine, 10 mg nifedipine, 10 mg nitrendipine and 2.5 mg verapamil to 10 adult male dogs intracavernosally, each at different times. Intracavernous pressure values, systemic arterial pressure values and heart rate values were recorded for 45 minutes after the intracavernosal injections. We used "paired student-t test" for statistical analysis.
Papaverine induced full erection in all of the 10 dogs. Nifedipine induced full erection in 4, nitrendipine in 5, and verapamil in 6 of the 10 dogs. Nifedipine and nitrendipine caused significant decreases in blood pressure and increases in heart rates.
In conclusion, the effects of intracavernosal CCBs are not superior than those of papaverine. We can not recommend nifedipine and nitrendipine for intracavernosal injections, but verapamil may be included in intracavernous pharmacotherapeutic combinations.

Key words: Penile erection, intracavernous injection, nifedipine, nitrendipine, verapamil.

Relaxation of the smooth muscles in corpora cavernosa is the key mechanism of penile erection[1] Smooth muscle relaxing agents can be administered intracavernosally for the diagnosis and treatment of erectile dysfunction. Papaverine, phentolamine and prostaglandin E1 are the widely accepted ones[2].

Smooth muscle relaxation can be achieved either by increasing intracellular cyclic guanosine monophosphate (cGMP) or cyclic adenosine monophosphate (cAMP) formation or by inhibiting the influx of calcium (Ca^{++}) across the cell membrane or by opening the potassium (K^{+}) channels[3-6]. An ideal intracavernosal pharmacotherapeutic agent should have rapid action with minimal side effects. Effectiveness of many of smooth muscle relaxing agents, including calcium channel blockers (CCBs), on corpus cavernosum smooth muscle have been shown at least in invitro settings[1,7,8]. However, we still don't have enough information about the invivo applications of many of these agents[9]. This experimental study

was designed to determine and compare the safety and effectiveness of intracavernosal injection of three different CCBs (nifedipine, nitrendipine and verapamil) and papaverine in dogs. Nifedipine is a dihydropyridine analog and one of the selectively acting CCBs. Nitrendipine is a newly developed dihydropyridine analog, with a longer plasma half life. Verapamil is a non-selectively acting CCB and has adrenoceptor antagonistic effect also[10].

Dogs are the best models for pharmacologic erection studies, because they have a pair of cavernous bodies hemodynamically independent from each other, so that one of them can be used as control[11].

MATERIALS AND METHODS

The study was performed in 10 adult healthy male mongrel dogs weighing between 27-35 kg. The effects of intracavernosal papaverine, nifedipine, nitrendipine and verapamil on cavernous pressure, arterial pressure and heart rate, were tested in each dog. At least 2 weeks long intervals were left between two injections in each dog.

Preparation of the dogs: Anesthesia was induced with intravenous 25 mg/kg sodium pentobarbital and the dogs were placed on the operation table. The hairs around the scrotum and penis were shaved. Intravenous saline infusion of 5 ml/kg/h and when necessary bolus infusion of 50 mg of pentobarbital maintained throughout the study. Left femoral artery was cannulated for blood pressure monitoring. Two 19-gauge scalp vein needles were placed into the proximal portion of both corpora just beneath the scrotum and connected to a Harvard Polygraph to record the intracavernous pressure. Intravenous 2000 U heparin infused to prevent coagulation in the catheters. Left femoral arterial catheter and precordial electrodes were connected to a Kontron monitor to record blood pressure and heart rate.

Pharmacologic agents and intracavernous injection: Intracavernous administrations of 30 mg papaverine, 10 mg nifedipine, 10 mg nitrendipine and 2.5 mg verapamil were performed respectively with 2 weeks intervals at least. The doses of the drugs studied were adapted from their optimal recommended doses for humans. Nifedipine and nitrendipine were dissolved in ether and prepared for injection in our Pharmacology Department. Injections were made slowly via a 30 G needle and 1 ml in volume, from the anterior site of the scrotum into only one of the cavernous bodies.

Recordings and parameters: Intracavernous pressure, heart rate and arterial prassure were monitorized for 60 minutes beginning from just before the intracavernous injection. Values of each parameter at the beginning and at the 3rd, 5th 15th, 30th and 45th minutes were recorded. Intracavernous pressure exceeding 90 % of the arterial pressure was accepted as full erection and those erections exceeding 45 minutes were accepted as prolonged erections[12]. Exclusion criteria was the development of an erection at the uninjected corpus during the study. Catheters and needles were removed at the end of each procedure and compressions, minimum for 5 minutes, were applied in order to prevent bleeding and hematoma formation.

Statistical analysis: Mean values and standard deviations of three parameters for each drug were calculated. Differences at 3rd, 5th, 15th, 30th and 45th minutes were compared with paired student-t test.

RESULTS

Intracavernous pressure and erection: Intracavernosal 30 mg papaverine induced full erection in all 10 dogs. Erections persisted for more than 45 minutes in 5 and resolved with cavernosal aspirations. The shortest duration of erection with papaverine was 20 minutes. All of the intracavernosal pressure increases recorded in 45 minutes were found statistically significant

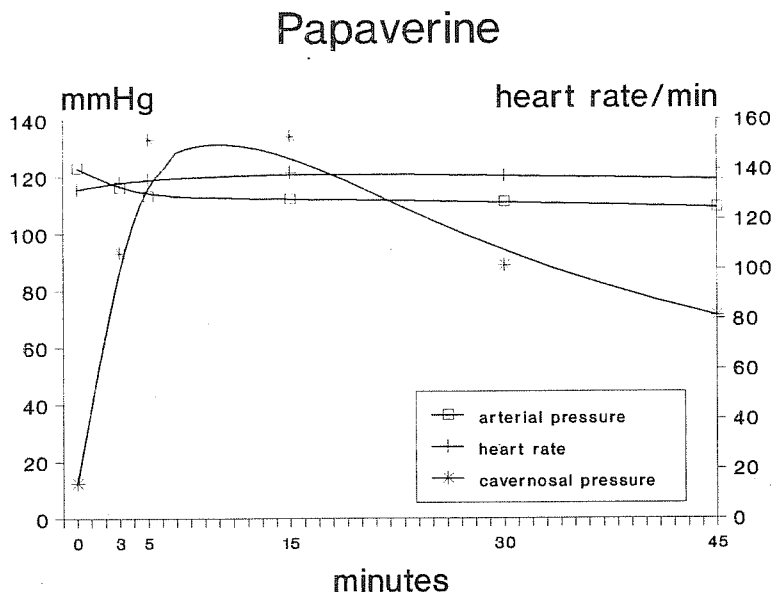

Figure 1 : Graphical representation of the mean values of intracavernous pressure, arterial pressure and heart rate after intracavernosal injection of papaverine in dogs.

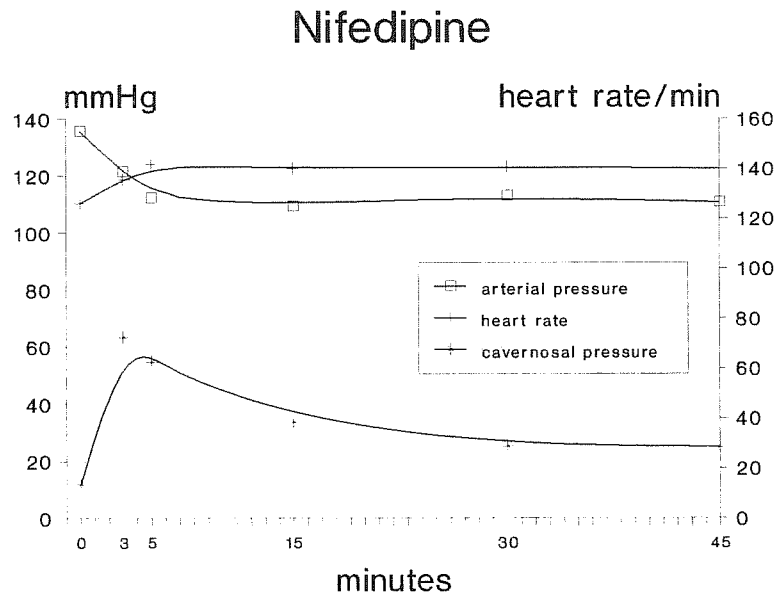

Figure 2 : Graphical representation of the mean values of intracavernous pressure, arterial pressure and heart rate after intracavernosal injection of nifedipine in dogs.

($p<0.05$) (Figure 1). Full erection occured in 4 of 10 dogs after intracavernosal injection of 10 mg nifedipine. Only one persisted for more than 45 minutes and then resolved with cavernosal aspiration. Shortest duration of erection after nifedipine was 5 minutes. Intracavernosal pressure increases at 3rd and 5th minutes were found statistically significant ($p<0.05$) (Figure 2). Intracavernosal 10 mg nitrendipine induced full erection in 5 of 10 dogs. The longest duration of erection with nitrendipine was 25 minutes and the shortest was 5 minutes. Intracavernosal pressure increases at 3rd and 5th minutes were found statistically significant ($p<0.05$) (Figure 3). Full erection occured in 6 of 10 dogs after intracavernosal injection of 2.5 mg verapamil. The longest duration of erection with verapamil was 30 minutes and the shortest was 5 minutes. Intracavernosal pressure increases at 3rd, 5th and 15th minutes were found statistically significant ($p<0.05$) (Figure 4).

Arterial pressure: Arterial blood pressure values were recorded as "mean arterial pressure" from the left femoral arteries of the dogs. Changes at the arterial blood pressure after the intracavernosal injections are listed in Table 1.

Heart rate: Significant increases in the heart rates were seen after intracavernosal nifedipine and nitrendipine injections. Mean values and statistical analysis of the heart rate differences after the injections are listed in Table 2.

Table 1: Statistical analysis and mean values of the changes in arterial pressure of the dogs after intracavernosal injections.

Drug	3rd minute	5th minute	15th minute	30th minute	45th minute
Papaverine	-7.0(±2.2) ($p<0.05$)	-11.0(±2.1) ($p<0.01$)	-11.0(±3.6) ($p<0.02$)	-12(±3.3 ($p<0.01$)	-14(±3.4) ($p<0.01$)
Nifedipine	-14.3(±3.7) ($p<0.001$)	-23.6(±5.1) ($p<0.001$)	-26.4(±3.6) ($p<0.001$)	-25.0(±4.1) ($p<0.001$)	-22.9(±6.9) ($p<0.02$)
Nitrendipine	-15.0(±3.3) ($p<0.01$)	-19.3(±4.3) ($p<0.01$)	-22.1(±3.3) ($p<0.001$)	-24.3(±7.4) ($p<0.02$)	-28.6(±5.7) ($p<0.01$)
Verapamil	-6.4(±3.3) ($p<0.05$)	-12.1(±5.1) ($p<0.05$)	-12.1(±7.6) ($p<0.05$)	-12.1(±6.1) ($p<0.05$)	-10.0(±4.1) ($p<0.05$)

Table 2: Stastical analysis and mean values of the changes in heart rate of the dogs after intracavernosal injections.

Drug	3rd minute	5th minute	15th minute	30th minute	45th minute
Papaverine	+2.8(±1.4) ($p<0.05$)	+3.6(±1.3) ($p<0.05$)	+6.0(±2.8) ($p<0.05$)	+4.6(+2.6) ($p>0.05$)	+3.0(±2.1) ($p>0.05$)
Nifedipine	+19.7(±5.4) ($p<0.02$)	+15.7(±17.9) ($p>0.05$)	+14.1(±16.1) ($p>0.05$)	+14.6(±11.6) ($p>0.05$)	+14.0(±9.5) ($p>0.05$)
Nitrendipine	+15.5(±5.3) ($p<0.05$)	+24.9(±7.1) ($p<0.02$)	+15.1(±7.1) ($p>0.05$)	+24.9(±13.0) ($p>0.05$)	+20.0(±7.8) ($p<0.05$)
Verapamil	+0.6(±1.8) ($p>0.05$)	+0.6(±2.7) ($p>0.05$)	+6.3(±2.2) ($p<0.05$)	+0.3(±2.2) ($p>0.05$)	-0.6(2.4) ($p>0.05$)

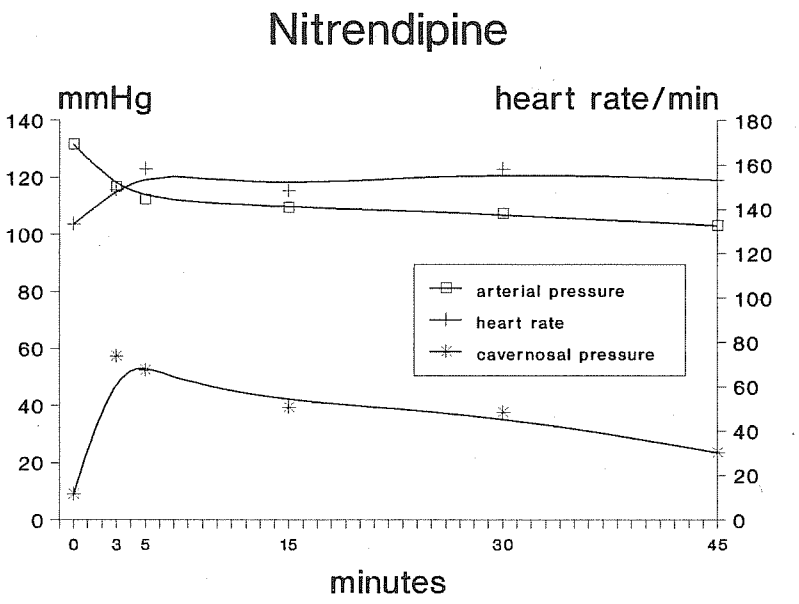

Figure 3 : Graphical representation of the mean values of intracavernous pressure, arterial pressure and heart rate after intracavernosal injection of nitrendipine in dogs.

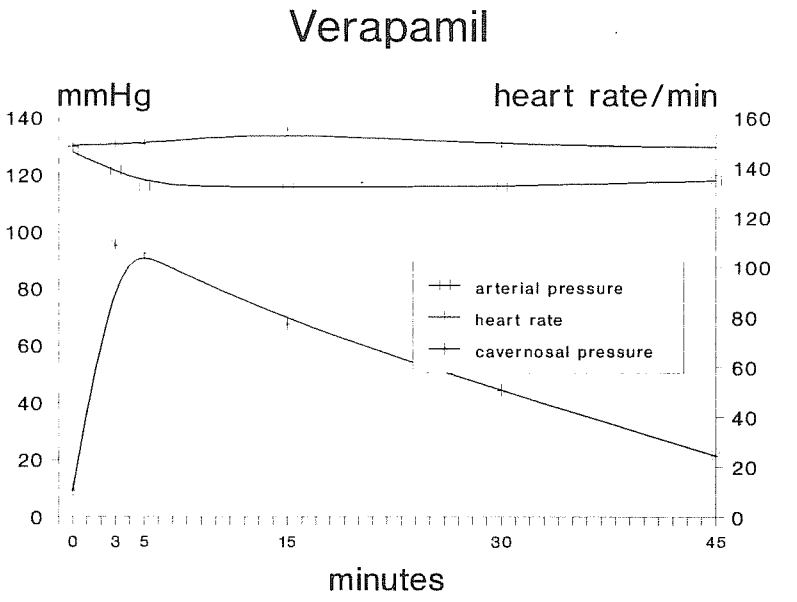

Figure 4 : Graphical representation of the mean values of intracavernous pressure, arterial pressure and heart rate after intracavernosal injection of verapamil in dogs.

DISCUSSION

Intracellular Ca^{++} is mandatory for the initiation and maintenance of smooth muscle contraction. CCBs are the drugs that inhibit the influx of Ca^{++} across the cell membrane by blocking voltage dependent or receptor mediated calcium channels[10]. Using cavernosal strips in invitro settings, their effectiveness and mechanisms of actions were well documented[7,8]. Our results showed that CCBs can induce erection when used intracavenosally, but they are not as effective as papaverine in recommended doses. Verapamil was found to be more potent in producing erection than nifedipine and nitrendipine. This can be attributed to the additional alpha-adrenoceptor blocking action of verapamil[8].

There were no previous recommended doses of CCBs for intracavernosal application. Therefore, we administered their optimal doses recommended for systemic use. The recommended intracavernosal dose of papaverine in dogs ranges between 5-15 mg [13]. We have injected 30 mg of papaverine and probably this was the reason of high occurence of prolonged erections in our study. With this higher dose, papaverine didn't cause significant decreases in the arterial pressure as significant as nifedipine and nitrendipine did. Nifedipine and nitrendipine caused significant decreases in blood pressure and increases in heart rates although used in optimal doses. These serious cadiovascular side efects suggest that these drugs were released into the systemic circulation because of the lack of the prompt and sustained relaxation of the cavernous smooth muscle and efficient activation of the veno-occlusive mechanism. Other reasons for these side effects may be the longer plasma half lives and lack of the local metabolisms of these agents. Prostaglandin E1 is the only drug that is known to be metabolised in corpus cavernosum[14].

There are conflicting reports about the effects of orally administered CCBs on penile erection in the literature. Some of the authors included them in the drugs which cause erectile dysfunction[15]. Others reported improvement in erectile function with oral nitrendipine[16]. Despite these conflicting reports, erectile potentials of CCBs should be kept in mind in the treatment of hypertension.

Another question that should be answered in our study was, how the intracavenous pressure could increase much more than the arterial pressure. This phenomen was explained by the contraction of striated muscles in men[1]. But there were no role of striated muscles during the pharmacologic erection especially in dogs. Further increase in the intracavernous pressure can be explained by stretched elastic fibers of tunica albuginea and cavernous skeleton during initiation of erection[17].

Cavernous smooth muscle relaxation is effected through a complex biochemical pathway, and a defect in any step of this pathway may result in erectile dysfunction [18]. Therefore, intracavernous pharmacotherapeutic combinations which include agents each acting at a different step will be the most effective and reliable alternative in the diagnosis and treatment.

In conclusion, CCBs induce penile erection when given intracavernosally. However, they are not as effective as papaverine. Verapamil is the safest and the most effective one amongst the CCBs we have studied. Therefore, verapamil may have a place in intracavernous pharmacotherapeutic combinations. Further invivo studies should investigate the dose-response and pharmacokinetics of intracavernous verapamil.

ACKNOWLEDGEMENTS

The authors wish to thank Bayer AG for providing purified nitrendipine and nifedipine; and also wish to thank Dr. Sedef Gidener who prepared the injectable forms of these agents.

Received : 24.04.1996
Accepted for publication : 06.05.1996

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