The action of a calcium channel blocker (verapamil) on gallbladder contractions in humans

Kalsiyum kanal blokerlerinin (verapamil) safra kesesi kontraksiyonuna etkisi

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SUMMARY: *While the inhibiting action of calcium antagonists on the gastrointestinal motility is well documented, its action on the biliary tract has not been extensively studied, despite its potential clinical usefulness. Twenty healthy volunteers participated in this study. The gallbladder volumes were measured using ultrasonography. After the baseline measurement, the subjects received 80 mg of verapamil (n=10) or placebo (n=10) per oral in the morning 1 h before rescanning. The gallbladder was rescanned in 15 min intervals for 60 min. At the end of this period all the volunteers received a standard liquid test meal (Ensure®), and then scans were performed again. Verapamil increased the fasting gallbladder volume to a maximum of 61.2% to 74.2% compared to the baseline (p<0.05) and of 49.1%-62.6% compared to the placebo group (p<0.05). Besides, the postprandial gallbladder volume increased to a maximum of 4.6%-61.2% compared to the baseline (p<0.05) in the first 30 min. Then it decreased to the baseline value. The gallbladder volume of the verapamil group was increased to a maximum of 86.8%-111.7% compared to the placebo group (p<0.05 and 0.01). These results demonstrated that verapamil significantly increased fasting and postprandial gallbladder volume.*

Key words: Calcium channel blocker, verapamil, gallbladder contraction, human

ÖZET: *Kalsiyum kanal blokerlerinin düz kas kontraktilitesini azalttığının gösterilmesinden sonra safra kesesi motilitesi için çok az sayıdaki deneysel çalışmaya konu olmuştur. Bu amaçla planlanan çalışmalarda elde edilen sonuçlarla kalsiyum kanal blokerlerinin kullanım alanının kardiyovasküler ve nörolojik hastalıklar yanında gastrointestinal sisteme de genişletilmesine imkan sağlayabileceği düşünülmüştür. Bu çalışmada gönüllülerin safra kesesi hacim ve alanları 12 saatlik açlıktan sonra ultrasonografi ile ölçüldü (n=20). Takiben kişilere plasebo veya 80 mg verapamil oral tb verilerek 2 saat sonra 15 dakika ara ile bir saat boyunca aynı ölçümler tekrarlandı. Standart test yemeğinden (Ensure®) sonra bir saatlik ölçümlere geçildi. Verapamil safra kesesi hacmini bazale göre % 61.2-74.2 (p<0.05), kontrol grubuna göre % 49.1-62.6 (p<0.05) oranında arttırdı. Verapamil postprandial volümü önemli ölçüde etkiledi ve ilk 30 dk kontrol bazal değerlerden % 4.6-61.2 (p<0.05) oranında yükseldi. Daha sonra bazal değere ve bir saat içinde de kontrole göre % 86.8-111.7 (p<0.05-0.001) yüksek kaldı. Bu sonuçlar verapamilin safra kesesi volümünü arttırdığını göstermektedir.*

Anahtar sözcükler: Kalsiyum kanal blokeri, verapamil, safra kesesi kontraksiyonu, insan

The class of calcium antagonists is constituted by pharmacological agents which inhibit the contraction evoked by extracellular calcium in depolarized smooth muscles (1). This action results from a selective interaction with calcium channels associated with the pericellular membrane.

Nifedipine, a calcium channel blocker, has been observed to decrease the basal pressure of the sphincter of Oddi, to lower the amplitude, to shorten the duration, and to decrease the contraction frequency of the sphincter in healthy volunteers (2), and these effects are even more pronounced in patients suffering from sphincter of Oddi dyskinesia (2). Patients with sphincter of Oddi dyskinesia often have an impaired emptying of the biliary tree shown in cholecystography, which can be improved by nifedipine. Nifedipine diminishes biliary pain (3). According to one study, nifedipine reduces the contractility of the gallbladder (4).

The inhibiting action of calcium antagonists on the gastrointestinal motility is well documented. Despite its potential clinical usefulness, its action on the biliary tract has not been clearly documented. Therefore, we investigated the effect of a calcium channel blocker (verapamil) on fasting gallbladder volume in normal subjects.

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Table 1. Effect of verapamil and placebo on gallbladder (volume/mL)

	Mean volume in different time (X±SEM)										
Groups	Baseline	60	75	90	105	Ens.	120	135	150	165	180
Verapamil		28.5±9.7*	30.4±13.2*	30.4±12.8*	30.8±11.6*T		30±12*	28.5±8.1*TT	23.4±8TT	18.5±7.1TT	16.4±7.3TT
Control	17.7±10.3	17.7±10.3	19.1±12.2	20.4±10.8	19±10.1		19.2±10.2	14.3±7.5	11.1±7.5	8.8±5.6	8.4±5.6

*p<0.05 difference from baseline
T: p<0.05, TT: p<0.01 difference from control

MATERIAL AND METHODS

Twenty healthy volunteers (mean age 48±11 years all within ± 12% of ideal body weight) agreed to participate in the study after the protocol and the test procedures had been explained to them. All the subjects completed the protocol. Scans were performed at 9:00 AM after a 12 h fasting. After the basal measurement was taken, the volunteers received either 80 mg verapamil (n=10) or placebo (n=10) per oral 1 h before rescanning.

The gallbladder was rescanned in 15 min intervals for 60 min. At the end of this period, all the volunteers received a standard liquid test meal (Ensure®) (375 cal/250 mL, protein 16.7%, fat 30%, carbohydrate 53.3%) and then scans were repeated.

The gallbladder volumes were measured by ultrasonograph (5). Real-time ultrasound scans were obtained with Siemens sonoline SL-2 using a 3.5 or 5 MHz transducer. The subjects were scanned supine in the right anterior oblique position by a radiologist trained in ultrasonography. The gallbladder was visualized in the longitudinal and transverse planes, and measurements of the maximum length, width, and height were taken in duplicate. The volume of the gallbladder was subsequently calculated using the ellipsoid method (volume=0.52×length×width×height).

The results were expressed as mean ± SEM unless otherwise stated. For statistical analysis, the Wilcoxon matched pairs signed-rank test or the Wilcoxon U test was used where appropriate. The level of significance was set at $p<0.05$.

RESULTS

The administration of verapamil increased the fasting gallbladder volume to a maximum of 61.2%-74.2% compared to the baseline ($p<0.05$) and of 49.1%-62.6% compared to the placebo group ($p<0.05$) (Figure 1). In the verapamil group, significant changes in the postprandial gallbladder volumes were observed. The postprandial gallbladder volume increased to a maximum of 4.6%-61.2% compared to the baseline ($p<0.05$) in the first 30 min, then decreased to the baseline value. In the verapamil group, the gallbladder volume was increased to a maximum of 86.8%-111.7% compared to placebo group ($p<0.05$ and 0.01) (Table 1) (Figure 1).

No side effects were reported by the subjects when 80 mg verapamil was taken.

DISCUSSION

The significant inhibitory effect of a calcium channel blocker on human gallbladder emptying, as demonstrated in the present study, is in agreement with previous observations (2, 4) but not with others which had suggested that a significant effect of a calcium channel blocker on ceruletide-induced gallbladder contraction (6).

The gallbladder volume in the interdigestive state is a result of: 1) hepatic bile secretion, 2) condensation of bile within the gallbladder, 3) gallbladder contractility and, 4) sphincter of Oddi contractility.

No information is available concerning whether calcium channel blockers could affect the postprandial release of cholecystokinin (CCK) and whether other gastrointestinal hormones are involved in the regulation of gallbladder contractility (7, 8). Nevertheless a calcium channel blocker (nifedipine) at an oral dose was demonstrated to significantly decrease the basal and submaximal pentagastrin or meal-stimulated gastric acid secretion without affecting the postprandial gastrin release (9, 10). Since a CCK output stimulated by duodenal acidification would be expected, the decreased acid load may cause a decrease in postprandial gallbladder emptying (4). According to another study, a significant rise in plasma CCK occurs within 20 min postprandially and reaches its maximum 40 min after a meal stimulus (11). Accordingly, it was just 30 and 40 min after the test meal ingestion when an inhibitory effect on

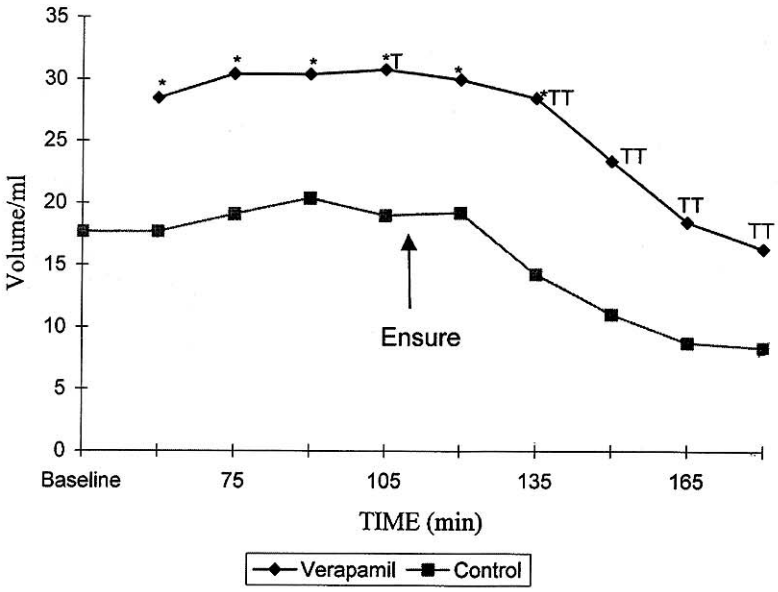

Figure 1. The mean volume in different time. *p<0.05 difference from baseline T: p<0.05, TT: p<0.01 difference from control

meal-induced gallbladder emptying was observed. Finally, an interference of nifedipine with the CCK effect on the gallbladder muscle can be excluded on the basis of *in vitro* experiments using whole guinea pig gallbladders (4), involving cat gallbladder muscle strips (12, 13). These authors demonstrated that CCK contracts the gallbladder muscle by mobilizing calcium from intracellular stores. Since calcium channel blockers influence the influx of extracellular calcium into smooth muscle cells, they would not be expected to affect the CCK-induced gallbladder contraction. This hypothesis was corroborated in the controlled double-blind human study (6).

The findings of the present study suggest that verapamil could be useful in the management of excessive gallbladder contractions in patients suffering from a functional gallbladder dysmotility. On the other hand, in patients requiring a prolonged calcium channel blocker treatment for cardiovascular reasons, a potential risk of gallstone formation due to impaired gallbladder motility should be taken into consideration.

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