The Action of a Calcium Channel Blocker (Verapamil) on Gallbladder Contractions in Humans

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Objective: **The class of calcium antagonists is constituted by pharmacological agents which inhibit the contraction evoked by extracellular calcium in depolarized smooth muscles. 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. Therefore we investigated the effect of a calcium channel blocker (verapamil) on fasting and postprandial gallbladder volume in normal subjects.**
Method: **Twenty healthy volunteers participated in this study. The gallbladder volumes were measured using ultrasonography. After the baseline measurement was taken, the volunteers received 80 mg of verapamil (n:10) or a placebo (n:10) per oral in the morning one 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.**
Results: **The administration of 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 ($p<0.05$). 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 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).**
Conclusion: **These results demonstrated that verapamil significantly increased fasting and postprandial gallbladder volume.**

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

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.

The calcium channel blocker nifedipine has been observed to decrease the basal pressure of the sphincter of Oddi, lowering the amplitude, shortening the duration, and decreasing the frequency of sphincter of Oddi contraction 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 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.

Material and Method

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. Ultrasound examination was performed at 9 am after a 12 hrs. fasting. After the basal measurement was taken the volunteers received either 80 mg verapamil (n:10) or a placebo (n:10) per oral in the morning one hour 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 performed again.

The gallbladder volumes were measured using ultrasonography. Using a 3.5 or 5 MHz transducer real time ultrasound scans were obtained with Siemens sonoline SL-2. The subjects were scanned supine in the right anterior oblique position by a radiologist experienced 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 x length x width x height) (5).

The results were expressed as mean ± SEM unless otherwise stated. For statistical analysis, the Wilcoxon matched pairs signed-rank test or the Mann-Whitney U test was used where appropriate.

Table I. Effect of verapamil and placebo on gallbladder volume/ml.

Groups	The Mean Volume in Different Time (X±SEM) (min)										
	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± 8^{TT}	18.5± 7.1^{TT}	16.4± 7.3^{TT}
CONTROL	17.7±10.3	17.7± 10.3	19.1± 12.2	20.4± 10.8	19± 10.1		19.2± 10.2	14.37.5	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

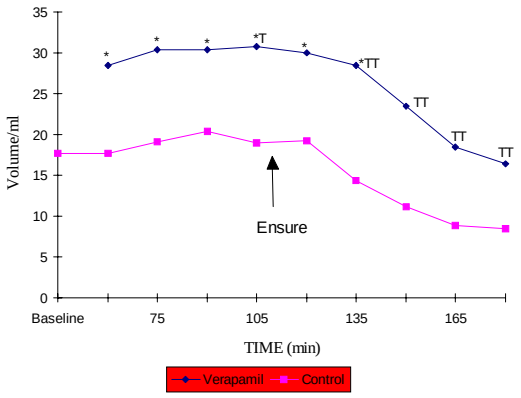

Figure 1. The mean volume in different times.

**p<0.05 difference from baseline*

^{T}p<0.05, ^{TT}p<0.01 difference from control

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 it decreased to the baseline value. In the verapamil group the gallbladder volume was increased to a maximum of 86.8%-111.7% compared to the placebo group (p<0.05) (Table I) (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 some 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 oral calcium channel blocker (nifedipine) 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 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 influenced 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 dismotility. 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.

References

1. Goldfraind T, Morel N and Wibo M: The heterogenecity of calcium movements in cardiac and vascular smooth muscle cell. Scand J Clin Lab Invest. 46 (suppl.180): 29-40, 1986.
2. Guelrud M, Mendoza S, Rossiter G, Ramirez L, Barkın J: Effect of nifedipine on sphincter of Oddi motor activity: Studies in healthy volunteers and patients with biliary dyskinesia. Gastroenterology 95: 1050-1055, 1988.

3. Sand J, Nordback I, Koskinen M, Matikainen M and Lindholm TS: Nifedipine for supperent Type II sphincter of Oddi dyskinesia. Am J Gastroenterol 88: 530-535, 1993
4. Jonderko K, Nowak A, Jonderko KJ, Sliwinks Z, and Kucioc C. Effect of nifedipine on interdigestive gallbladder emptying in man. Dig dis Sci 36: 1430-1440, 1991.
5. Everson GT, Browerman DZ, Johnson MJ, Kern FJR: A critical evaluation of real-time ultrasonography for the study of gallbladder volume and contraction Gastroenterology 79: 40-46, 1980.
6. Porschen R, Pieper S, Bernhardt L, Schade B, Wienbeck M: In vivo effects of nifedipine and BAY I 8201 on ceruletide induced gallbladder contraction. Gastroenterol 26: 755-761, 1988.
7. Banfied WJ: Physiology of the gallbladder. Gastroenterology 69: 770-777, 1975.
8. Baxter JN. Gallbladder emptying. J Gastroenterol Hepatol 4: 353-372, 1989.
9. Caldara R, Masci E, Barbieri C, Sorghi M, Piepoli V,Tittobello A: Effect of nifedipine on gastric acid secretion and gastrin release in healthy man. Eur J Clin Pharmacol 28: 677-679, 1985.
10. McColl KEL, Buchanan NMM, Laferla G, Hearns J, Buchanan K, Crean Gp: Effects of nifedipine on gastric acid gastrin release in man. Gut 28: 455-459, 1987.
11. Hopman WPM, Jansen JPMJ, Rosenbusch G, Lamers CBHW: Cephalic stimulation of gallbladder contraction in humans: role of cholecystokinin and the cholinergic system. Digestion 38: 197-203, 1987.
12. Pomeranz IS, Davison JS, Shaffer EA: Effect of chlorpromazine (CPZ) on cholecystokinin-induced gallbladder contraction: the role of calcium. Isr J Med Sci 24: 275-281, 1988.
13. Lee KY, Biancani P, Behar J: Calcium sources utilized by cholecystokinin and acetylcholine in the cat gallbladder muscle. Am J Physiol 256: G785-G788, 1989.

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