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RESEARCH ARTICLES / BILIMSEL ARAŞTIRMALAR

Comparison of the Release and Pharmacodynamic Characteristics of a Formulated and Commercial Sustained-Release Verapamil Tablets

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Formulasyonu Yapılmış ve Ticari Denetimli Salım Tabletlerinin Salım ve Farmakodinamik Özelliklerinin Kıyaslanması

Özet: Kontrollu salım gösteren bir verapamil tableti formüle edilmiş ve kontrollü salınan bir piyasa tableti ve plasebo ile, elektrokardiyografik sonuçları kullanarak, farmakodinamik olarak karşılaştırılmıştır. Çalışma oniki gönüllü üzerinde yapılmıştır.

Anahtar Sözcükler : Verapamil hidroklorür, Denetimli Salım Gösteren Tabletler, Formülasyon, Klinik Değerlendirme

Summary: A sustained-release tablet of verapamil was formulated and evaluated pharmacodynamically in man, using electrocardiographic results, with comparison to a commercially available sustained-release verapamil tablet and a placebo. Twelve volunteers were involved in the study.

Key Words : Verapamil Hydrochloride, Sustained-Release Tablets, Formulation, Clinical Evaluation.

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Introduction

Verapamil, a papaverine derivative, is a slow calcium channel blocker belonging to the phenylalkylamine class[1,2]. It exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial muscle as well as in conductile and contractile myocardial cells[1,3-5].

Initially introduced in Europe as a coronary vasodilator in 1962[6], verapamil was first used in the United States for the treatment of supraventricular tachycardia[7]. As a calcium channel blocker, this compound has vasodilatory as well as antiarrhythmic properties[8]. The usefulness of verapamil in the treatment of hypertension is due primarily to the vascular vasodilatory properties[9]. Direct coronary vasodilation, along with a depression of cardiac muscular activity, which leads to a beneficial effect on myocardial oxygen supply/demand ratio, explains their usefulness in the treatment of angina[10-14]. Among the other calcium channel blockers, verapamil has been shown to have the greatest effect on the atrioventricular node refractory period.This is the main mechanism of action for the effect of verapamil on supraventricular tachycardia[15-17].

Several investigators have found a decrease in the maximum achievable heart rate[18-19] and a prolongation of the PR-interval or QT-interval on the surface electrocardiogram due to a delay in atrioventricular conduction, as cardiac alterations in men[8, 20-24].

When the pharmacologic activity of a drug is clinically desirable over a 24-hour period, and the

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drug has a short half-life, either an immediate-release formulation must be administered several times daily or a sustained-release formulation can be administered every 12 or 24 hours. Verapamil is a suitable candidate for a sustained-release formulation since it is readily soluble in water as hydrochloride and its elimination hal-life is quite short. On the other hand, the rate of hepatic first-pass metabolism of verapamil is high[20,25-27] which is often regarded as a disadvantage for a drug in sustained-release form[28]. However, it has been reported that no problem arises with verapamil at doses as low as those we use[29]. It was also shown by Marvola et al.[30] that absorption of verapamil occurs after 8 or 12 hr and verapamil has a short biological half-life of 5.3 hr, however use of a single-unit to deliver it at a controlled rate leads to no loss in bioavailability. Several attempts have been made to develop a sustained-release formulation of verapamil[20,22,23,29,30-34].

Large single doses of verapamil were reported to produce high peak concentrations in the blood but no prolongation of the duration of activity[20]. Therefore, 120 mg verapamil was formulated as a sustained-release tablet which is used commercially and only hints to the slow release were expected when designing a solid oral dosage form that has a sustained-release rate pattern in vitro.

The purpose of the study was to formulate a matrix tablet of verapamil hydrochloride and evaluate pharmacodynamically using electrocardiographic results and, in-vitro dissolution rate tests as compared to a commercially available sustained-release tablet and a placebo.

Materials and Methods

Materials

The following materials were used: Verapamil hydrochloride (Knoll, İstanbul, Türkiye), Eudragit RS (Röhm Pharma, Darmstadt, Germany), Lactose Fast-Flo (Foremost Food Company, San Fransisco, USA), Magnesium stearate (E. Merck, Leverkusen, Germany), 120 mg Verapamil hydrochloride sustained-release tablets (Isoptin KKH, Knoll, İstanbul, Türkiye). All other materials used were of analytical grade.

Methods

Preparation of Tablets

After pretesting the concentration of the matrix material, Eudragit RS, 15% of the total tablet weight was used. Sustained-release matrix tablets were formulated to contain 120 mg verapamil hydrochloride. In order to obtain a constant tablet weight, lactose was added as a filler. 2% magnesium stearate was incorporated as a lubricant prior to compression. After testing the direct compression method, wet granulation method was decided to be used since no satisfactory tablets could be obtained by direct compression. The powders were mixed and granulated using isopropyl alcohol:acetone (4:3). Tablets were compressed on a single-punch tablet machine Erweka Ar 400, with a tablet weight of 400 mg, using a flat nonbeveled punch, and the tablet hardness was maintained within the range of 6.5-7 kg on a Monsanto hardness tester.

In Vitro Release of Verapamil Hydrochloride From Tablets

The experimental formulation and the commercially available tablet, Isoptin KKH, were tested for dissolution rate in 600 ml of distilled water using the USP XXI Apparatus at 50 rpm. UV-spectrophotometric analysis was done on the samples collected at 0.5, 1, 2, 3, 4, 5, 6 and 7 hours. The calibration equation with $r = 0.999$ was used for the quantification of verapamil hydrochloride.

Clinical Studies

Twelve healthy volunteers (5 females, 7 males) were used for each group of drug administration of which the mean age is 30 with body weights of 44-90 kg (mean 67±23). Drug administration was performed according to placebo-controlled double blind randomized design.

After the administration of Isoptin KKH, our experimental tablet and the placebo, electrocardiographic parametrs, were recorded at time, 0, 6, 12 and 24 hours, including heart rate, QT-interval and the blood pressure.

Table 1. The Pharmacodynamic Results After the Administration of Isoptin KKH, Experimental Formulation and the Placebo.

Time	Isoptin KKH			Experimental Formulation			Placebo		
(hr)	Heart rate (beats/min)	Blood pressure (mm Hg)	QT Internal (sec)	Heart rate (beats/min)	Blood pressure (mm Hg)	QT Internal (sec)	Heart rate (beats/min)	Blood pressure mm Hg)	QT Internal (see)
0	73±8	117±12 68±8	0.35±0.03	74±12	116±4 74±4	0.36±0.02	77±10	118±12 70±7	0.35±0.02
6	71±6	115±10 67±5	0.36±0.01	73±11	119±13 75±11	0.35±0.03	77±15	121±10 73±8	0.35±0.03
12	69±7	120±10 71±5	0.37±0.02	72±10	120±11 73±10	0.37±0.02	77±18	120±11 74±14	0.35±0.03
24	67±7	93±23 67±10	0.37±0.02	69±12	120±10 73±8	0.37±0.02	72±14	115±9 74±5	0.36±0.04

Results and Discussion

In Vitro Release of Verapamil Hydrochloride From Tablets

Figure 1 shows the mean in vitro dissolution profiles of both Isoptin KKH, the commercial preparation, and our experimental formulation. The values given in this figure are the mean of three trials. Experimental formulation has reached 50 % release at about 2.5 hours while Isoptin KKH had a more extended profile with 50 % release at 4 hours. Preliminary studies have revealed that the criterion of acceptance for a sustained-release tablet could be 40-65 % release at 3 hr and 55-80 % release at 6 hr[31,35,36]. These two tablets seem to support this observation.

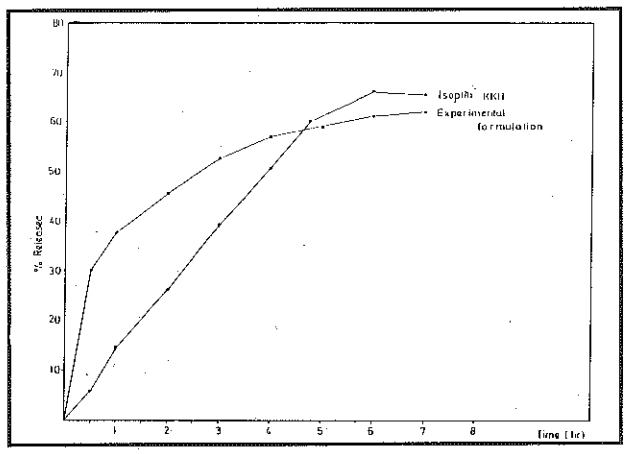

Figure 1. The Dissolution Profiles of Isoptin KKH and the Experimental Formulation.

Clinical Studies

Table 1 shows the heart rates, the blood pressures and QT-intervals after the administration of Isoptin KKH, experimental formulation and the placebo.

Mean blood pressure after the adminastration of Isoptin KKH decreased from 117/68 to 93/67 mm Hg while no significant decrease could be observed with our experimental formulation.

There was no statistically significant variance between the two formulations in pulse frequencies and QT-intervals ($p>0.05$). Mean heart rate decreased from 73 beats/min to 67 beats/min with Isoptin KKH. The corresponding values for our experimental formulation were 74 beats/min and 69 beats/min. At the end of the run-in period, the value of QT-intervals were 0.37 sec for both formulations. There is no prolongation of QT-intervals during a 24-hr period. Placebo, as could be predicted, showed no significant electrocardiographic changes.

No subject experienced any adverse reactions which could be attributed to the study medication.

The fate of 120-mg sustained-release tablets with greatly retarded absorption unequivocally proved the difficulty associated with sustained release

formulations of drugs having a high first-pass metabolism. There seems to be a concern about the studies presented perviously since no significant electrocardiographic results (except for the pulse frequency) could be obtained after the administration of a single dose of commercially available sustained-release tablet and experimental tablet. The problem stands for the oral adminastration of verapamil hydrochloride due to the inter- and intrasubject variation and in vivo pharmacodynamic results obtained after the administration of solid dosage forms that show sustained release in vitro. It can be concluded for oral verapamil that no in vitro-pharmacological effect correlation is present.

Other administration routes excluding the oral route seem to be superior concerning the bioavailability of verapamil. Nasal route is one of the alternatives and a study is being carried on in our laboratory to be reported soon.

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