Chapter 9
Haemodynamic study in rat

9.1 INTRODUCTION

Sumatriptan is a clinically effective anti-migraine, 5-$HT_{1B/1D}$ receptor agonists which acts via direct constriction of distended cranial and meningeal blood vessels (Humphrey & Feniuk, 1991) and/or inhibition of neuropeptide release from trigeminal sensory neurons innervating these blood vessels (Moskowitz, 1992). Sumatriptan, due to its vasoconstrictive nature, is reported to have cardiovascular side effects and is not preferred in cardiovascular patients. Serious cardiovascular events attributed to sumatriptan have most often been reported in patients at significant cardiovascular risk, or in overt cardiovascular disease. They also have occurred, however, in patients without evidence of cardiovascular disease. There are various reports of myocardial infarction due to subcutaneous administration of sumatriptan succinate (Anghileri et al, 2006; Erbilen et al, 2005; Ottervanger et al, 1993; Tomita et al, 2002). Hence it is important to study cardiovascular effects of intranasally administered sumatriptan succinate. There are no previous reports available relating to cardiotoxicity study for intranasally administered sumatriptan. The present chapter investigates cardiovascular effects of sumatriptan formulations in rats.

9.2 EXPERIMENTAL

9.2.1 Method

Male Sprague dawley rats (200 – 250 g) were anaesthetized with urethane (1.2 g/kg, i.p.) A midline incision was made; trachea was isolated and cannulated to facilitate breathing. Right common carotid artery was isolated and cannulated with PE catheter filled with heparinised saline. This PE catheter was connected to a precalibrated Biopac pressure transducer connected to Biopac MP-30 data acquisition system (BIOPAC systems, NY, USA). Biopac ECG electrodes were attached to forelimbs and hind limbs of rat as per lead II of ECG and connected to Biopac data acquisition system. After 15 min of stabilization period, drugs were administered by the desired route and haemodynamic parameters (Blood pressure, ECG and heart rate) were recorded using ACQ software (3.1 v, Biopac systems) for 2 hours after drug administration. Sumatriptan succinate solution was administered intranasally, subcutaneously

and intravenously. Sumatriptan formulations were administered intranasally using micropipette as described in the previous chapter All the haemodynamic parameters were evaluated using ACQ software.

9.2.2. Statistical analysis

All the data were expressed as mean ± SD (n=4 to 6), statistical calculations were done using Graph pad prism software using one way analysis of variance (ANOVA). Results were considered statistically significant when $P<0.05$.

9.3 RESULTS AND DISCUSSION

Effect of sumatriptan formulations on blood pressure, ECG (QT interval) and heart rate is shown in figure 9.4 and Table 9.2. As evident from the results intravenous administration of sumatriptan succinate caused death in 3 out of 6 animals under study with in 10-15 mins after sumatriptan administration; this may be due to severe coronary vasoconstriction leading to myocardial infarction. Hence it is not administered intravenously in clinical practice and sumatriptan package is marketed with a warning on label "not for intravenous use".

Sumatriptan is administered subcutaneously in further experiments as reported cases of severe myocardial infarction are less pronounced compared to intravenous administration. In the present study sumatriptan solution when administered intravenously caused significant changes in haemodynamics of rats, as evidenced by significant increase in blood pressure and QT interval and significant decrease in heart rate (Table 9 1, 9.2 and Figure 9.4). Further intravenous administration also caused 50% mortality in this group. No mortality was observed when sumatriptan was administered by any other route except intravenous. Subcutaneous administration caused increase in blood pressure and decrease in heart rate, which may be due to vasoconstrictor effect of sumatriptan succinate on $5HT_1$ receptors located in the vasculature, increase in blood pressure and decreased heart rate was reversed with time. Also increase in QT interval was seen only at 60 min which reversed with time and thus subcutaneous administration seems to be a comparatively safe in terms of cardiovascular toxicity. Moreover no mortality was observed when sumatriptan was

administered subcutaneously. A normal ECG pattern is shown in figure 9.1, QT interval was measured using ACQ software

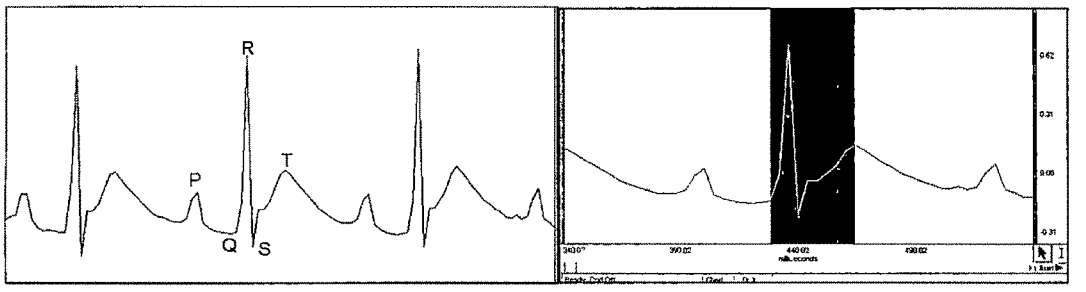

Figure 9.1: Normal ECG of rat

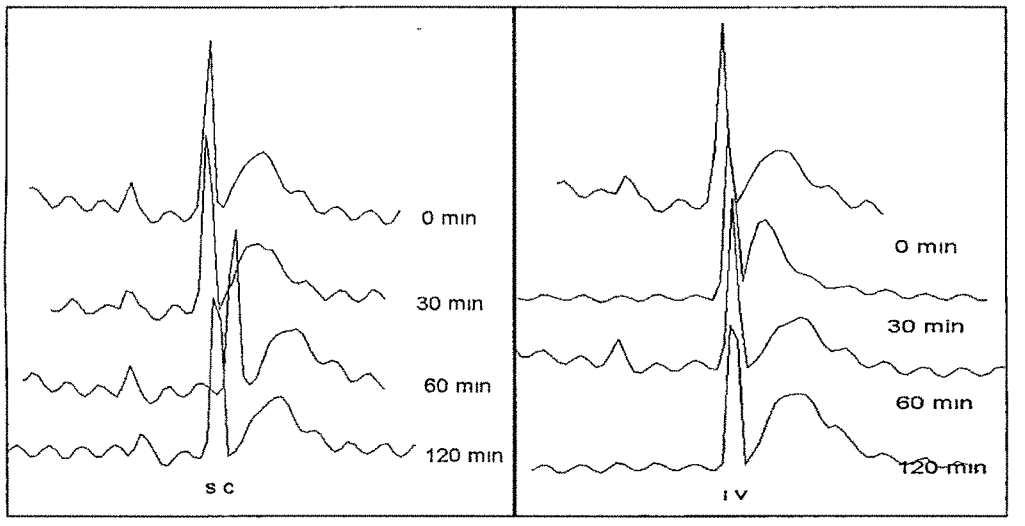

Figure 9.2 ECG pattern at different time interval after s.c and i.v administration of sumatriptan succinate in rats

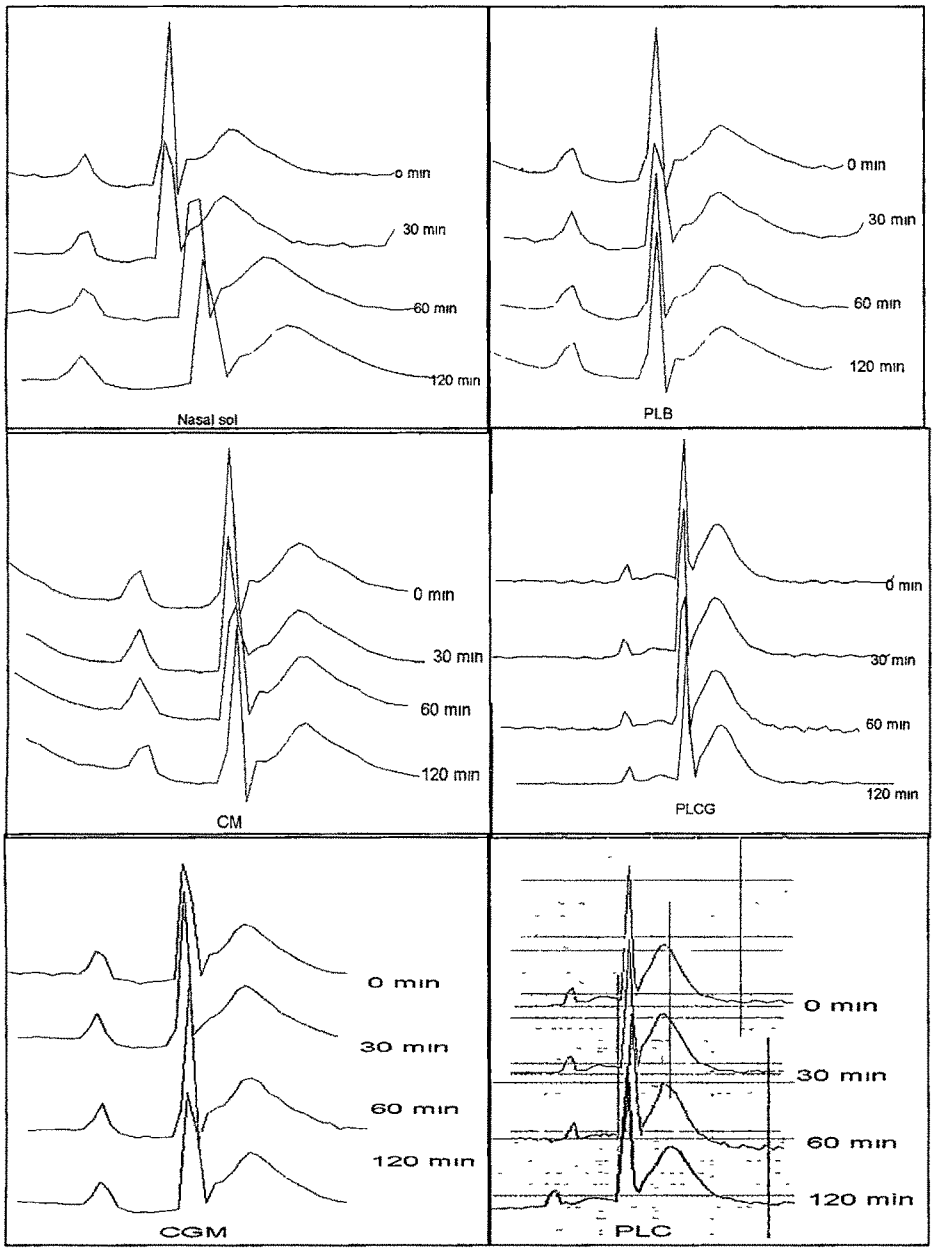

Figure 9.3 ECG pattern at different time interval after intranasal administration of various formulation. (PLB = Pluronic gel, CM = Carbopol microspheres, PLCG = Pluronic Carbopol chitosan glutamate gel, CGM = Chitosan glutamate microspheres, PLC = Pluronic carbopol gel)

As seen from the ECG of rats, administration of sumatriptan by i.v. caused significant alteration in ECG. The QT interval was prolonged, P wave was irregular and absent at some timepoints(figure 9.2).

Subcutaneous administration of sumatriptan succinate caused widening of the ECG and QT interval was increased at 60 minutes and was restored to normal at 120 minutes and hence haemodynamic change was considered insignificant (figure 9.2).

ECG changes with respect to time for all the intranasally administered formulations are shown in figure 9.3. When intranasal sumatriptan formulations were administered there were no ECG alterations. Results obtained from the study of blood pressure and heart rate revealed that there was no change compared to control animals (Figure 9.4 and Table 9.2). Intranasal administration of sumatriptan in the form of solution and various formulations had no significant effect on haemodynamics of rats compared to control group. This suggests that sumatriptan succinate administered by intranasal route can be safer option to reduce cardiovascular complications. Hence intranasal sumatriptan formulations showed no cardiovascular side effects that were observed by intravenous administration.

Table 9.1 Summary of haemodynamic changes due to sumatriptan administration by various routes.

Groups	Route	Mean Blood Pressure	Heart rate	QT interval	% Mortality
Control		-	-	-	**0**
Solution	i.v	↑↑	↓↓	↑↑↑	**50**
Solution	s c	↑	↓	↑	**0**
Solution	i.n.		↓		**0**
PLB	i.n.	-	-	-	**0**
PLC	i.n.	-	-	-	**0**
PLCG	i n.	-	-	-	**0**
CM	i.n.	-	-	-	**0**
CGM	i.n.	-	-	-	**0**

(i v.: intravenous, s.c.: subcutaneous, i.n.: ıntranasal, ↑ : Increase, ↓. decrease, - : No change)

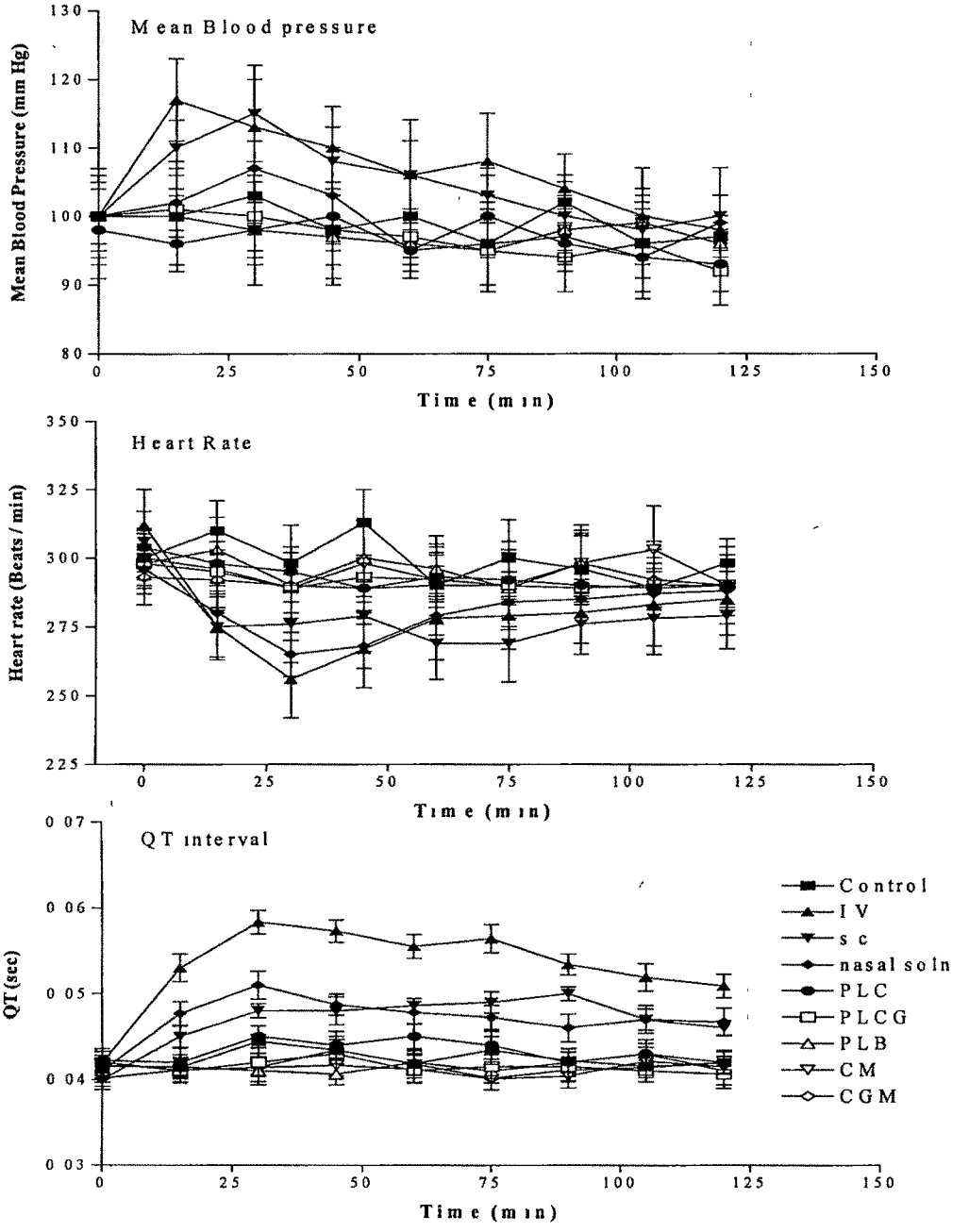

Figure 9.4. Effect of sumatriptan formulations on blood pressure, heart rate and QT interval in rats. All the values are expressed as mean ±SEM. (s.c. = subcutaneous, PLC = Pluronic carbopol gel, PLCG = Pluronic Carbopol chitosan glutamate gel, PLB = Pluronic gel, CM = Carbopol microspheres, CGM = Chitosan glutamate microspheres)

Mean Blood Pressure (mmHg)									
Time	**control**	**i.v.**	**sc**	**intranasal**	**PLC**	**PLCG**	**PLB**	**CM**	**CGM**
0	100 ± 5 7	100 ± 1 8	100 ± 5 5	100 ± 5 4	98 ± 7 7	100 ± 6 3	100 ± 5 4	100 ± 6 0	100 ± 6 1
15	98 ± 4 8	118 ± 6 2	110 ± 4 9	102 ± 6 2	96 ± 4 5	101 ± 3.8	100 ± 7 3	100 ± 3 9	100 ± 3 8
30	97 ± 6 2	113 ± 7 7	115 ± 7 4	107 ± 4 2	98 ± 4 3	100 ± 5 5	98 ± 8 0	98 ± 5 6	98 ± 5 5
45	98 ± 5 1	110 ± 6.3	108 ± 5 1	103 ± 7 2	100 ± 5 9	98 ± 4 9	97 ± 6 4	97 ± 7 4	97 ± 7 4
60	100 ± 6 7	106 ± 5 9	106 ± 8 2	95 ± 3 8	95 ± 4 8	97 ± 3 8	96 ± 4 3	96 ± 4 2	96 ± 3 6
75	96 ± 7 7	108 ± 7 1	103 ± 4 6	96 ± 6 7	100 ± 6 6	95 ± 5 1	95 ± 6 8	95 ± 5 7	95 ± 5 8
90	102 ± 3 9	104 ± 5 5	100 ± 6 8	97 ± 4 8	96 ± 4 5	94 ± 5 3	98 ± 3 7	98 ± 5 3	98 ± 5 8
105	96 ± 7 2	100 ± 7 4	98 ± 4 2	94 ± 6 1	94 ± 5 8	96 ± 5 3	99 ± 5 5	99 ± 5 1	99 ± 5 4
120	97 ± 4 1	98 ± 5 5	100 ± 7 2	99 ± 4 5	93 ± 6 3	92 ± 3 6	96 ± 4 1	96 ± 3 5	96 ± 3 7
Heart Rate (BPM)									
0	300 ± 10 5	312 ± 13 2	306 ± 11 6	296 ± 9 4	304 ± 10 3	298 ± 10 5	298 ± 11 8	300 ± 11 5	293 ± 10 7
15	310 ± 11 5	275 ± 11 8	275 ± 12 4	280 ± 7 7	298 ± 8 4	295 ± 10 6	303 ± 12 6	296 ± 14 2	292 ± 11 6
30	298 ± 14 7	256 ± 14 2	276 ± 14 5	265 ± 11 2	295 ± 10 6	289 ± 12 4	290 ± 11 2	289 ± 9 8	290 ± 14.1
45	313 ± 12 3	267 ± 14 5	279 ± 13 9	268 ± 8 6	289 ± 11 5	293 ± 10 3	300 ± 10 4	298 ± 14 5	289 ± 11 2
60	290 ± 12 8	278 ± 15 2	269 ± 13 4	279 ± 12 4	293 ± 12 4	292 ± 9.4	296 ± 12 8	292 ± 13 4	290 ± 14 3
75	300 ± 14 6	279 ± 12 3	269 ± 14 5	284 ± 10.3	292 ± 11 8	290 ± 12 4	289 ± 10 5	290 ± 16 1	290 ± 12.4
90	296 ± 12 1	280 ± 11 8	276 ± 11 3	285 ± 12 7	290 ± 10 5	289 ± 13 2	298 ± 14 2	298 ± 11 2	298 ± 12.3
105	289 ± 11.8	283 ± 15.4	278 ± 13 6	287 ± 11 8	289 ± 11 7	290 ± 10.3	292 ± 12 4	303 ± 16 3	292 ± 14 5
120	298 ± 9 8	285 ± 13 6	279 ± 12 1	288 ± 11 8	290 ± 9 7	290 ± 11 7	290 ± 14 3	290 ± 11 8	290 ± 11 7
QT interval (sec)									
0	0 0416 ± 0 0028	0 0420 ± 0 0030	0 0400 ± 0 0020	0 0410 ± 0 0032	0 0422 ± 0 0034	0 0420 ± 0 0032	0 0415 ± 0 0032	0 0402 ± 0 0032	0 0402 ± 0 0032
15	0 0414 ± 0 0030	0 0530 ± 0 0040	0 0450 ± 0 0030	0 0477 ± 0 0034	0 0420 ± 0 0040	0 0410 ± 0 0034	0 0415 ± 0 0034	0 0411 ± 0 0034	0 0411 ± 0 0034
30	0 0445 ± 0 0020	0 0583 ± 0 0034	0 0480 ± 0 0020	0 0510 ± 0 0040	0 0450 ± 0 0030	0 0420 ± 0.0040	0 0410 ± 0 0040	0 0414 ± 0 0040	0 0414 ± 0.0040
45	0 0434 ± 0 0040	0 0573 ± 0 0032	0 0480 ± 0 0040	0 0487 ± 0 0030	0 0440 ± 0 0040	0 0430 ± 0.0030	0 0406 ± 0.0030	0 0417 ± 0 0030	0 0434 ± 0.0030
60	0 0418 ± 0 0030	0 0555 ± 0 0034	0 0486 ± 0 0020	0 0478 ± 0 0032	0 0450 ± 0 0034	0 0410 ± 0 0032	0 0420 ± 0 0032	0 0412 ± 0 0040	0 0418 ± 0 0040
75	0 0434 ± 0 0040	0 0564 ± 0 0040	0 0490 ± 0 0030	0 0472 ± 0 0034	0 0440 ± 0.0040	0 0415 ± 0 0034	0 0410 ± 0 0034	0 0401 ± 0 0032	0 0402 ± 0 0032
90	0 0422 ± 0 0034	0 0534 ± 0 0030	0 0500 ± 0 0020	0 0460 ± 0 0040	0 0420 ± 0 0030	0 0415 ± 0 0040	0 0420 ± 0 0040	0.0404 ± 0.0034	0 0411 ± 0.0034
105	0 0415 ± 0 0032	0 0519 ± 0 0040	0 0470 ± 0 0040	0 0470 ± 0 0030	0 0430 ± 0 0040	0 0410 ± 0 0030	0 0430 ± 0 0030	0 0421 ± 0 0040	0.0414 ± 0.0040
120	0 0420 ± 0 0034	0 0509 ± 0 0034	0 0460 ± 0 0020	0 0467 ± 0 0040	0 0420 ± 0 0030	0 0406 ± 0 0040	0 0410 ± 0.0040	0 0415 ± 0 0030	0 0420 ± 0 0030

Table 9 2: Mean Blood Pressure, Heart rate and QT interval of rats treated with sumatriptan formulations. All the values are expressed as Mean ±SD.

9.4 COCNLUSION

Sumatriptan succinate administered intravenously showed 50% mortality rate within 15-20 minutes of administration, also there was signıficant increase in blood pressure and QT interval and sıgnificant decrease in heart rate. However subcutaneous administration showed 0% mortality with significant increase in blood pressure and significant decrease in heart rate, However ıt can be considered safe as there was no increase in QT interval. Intranasal formulations had no signıficant effect on haemodynamics in all respect as compared to control group and hence it could be concluded that intranasal adminıstration of sumatriptan succinate is better and safer alternatıve in terms of cardiotoxicity.

9.5 REFERENCES

Anghileri E, Toso V, Perini F (2006). Acute myocardial infarction after sumatriptan administration for cluster headache Neurol Sci.,26(6),456-9

Erbılen E, Ozhan H, Akdemir R, Yazıcı M (2005). A case of myocardial infarction with sumatrıptan use Pediatr Cardiol.,26(4),464-6

Ottervanger JP, Paalman HJ, Boxma GL, Stricker BH (1993). Transmural myocardial infarctıon with sumatriptan. Lancet, 3(341),861-2.

Tomita M, Suzukı N, Igarashı H, Endo M, Sakai F (2002). Evidence against strong correlation between chest symptoms and ıschemic coronary changes after subcutaneous sumatrıptan ınjectıon. Intern Med ,41(8), 622-5.

Humphrey, P P & Fenıuk, W. (1991). Mode of actıon of the anti- mıgraıne drug sumatriptan. Trends Pharmacol Sci , 12, 444 - 446.

Moskowitz, M.A. (1992). Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in mıgraıne Trends Pharmacol. Sci., 13, 307 - 311.