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Increased Oral Clearance of Metoprolol in Pregnancy

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Summary. The disposition of oral metoprolol was studied in 5 women during the last trimester of pregnancy and 3 to 5 months after delivery. After a single oral dose of 100 mg the individual peak plasma concentration in the pregnant state was only 20–40% of that after pregnancy. The plasma half-lives of metoprolol were about the same during (average 1.3 h) and after pregnancy (average 1.7 h). By contrast, the area under the plasma concentration versus time curve was much smaller *during* (mean 262 nmol/l × h) than *after* (mean 1298 nmol/l × h) pregnancy, resulting in an average apparent oral clearance (Cl_o) of metoprolol that was 4.4 times higher during (362 ml × kg^{-1} body-weight × min^{-1}) than after pregnancy. The increased Cl_o in pregnancy is assumed to be due to enhanced hepatic metabolism of the drug. The possible clinical consequence of the difference in the disposition of metoprolol is discussed.

Key words: metoprolol, pregnancy, hypertension; kinetics, pre-eclampsia

In the treatment of hypertension during pregnancy it is necessary to consider not only the mother but also any effect on the fetus and newborn infant. Cardioselective β-blocking agents in combination with hydralazine have been widely used in this group of patients in the past few years (Lindberg and Sandström 1981). Although the metabolic and cardiovascular effects of β-blocking agents have been the subject of several investigations, both in pregnant (Lunell et al. 1979) and non-pregnant women (Nilsson et al. 1978), very little is known about their kinetics in pregnant women.

The pregnant state is associated with several physiological and metabolic changes, which have been shown to affect the disposition of various drugs (Davison et al. 1970; Dam et al. 1979; Krauer and Krauer 1977). Drugs which are eliminated by renal excretion, such as ampicillin (Philipsson 1977) and lithium (Schou et al. 1973) have been particularly studied in this context. Here, the influence of pregnancy on the kinetics of oral metoprolol is reported. This drug is almost entirely eliminated by hepatic metabolism (Johnsson and Regårdh 1976).

Patients and Methods

Five women, aged 26–28 years, took part in the study; their clinical features are given in Table 1. None of the patients had proteinuria; 4 were normotensive at the beginning of the pregnancy, and Patient No. 1 had a blood pressure of 160/90 and might have been a borderline case of essential hypertension. The kinetics of orally administered metoprolol was studied in the last trimester of pregnancy, and between the 12th and 23rd week after delivery. Informed consent was obtained from all patients before the study. The investigation was approved by the Ethics Committees of the hospitals.

After hypertension had been detected, and informed consent obtained, the patients were given a single oral dose of metoprolol tartrate 100 mg. They were then treated until delivery with a combination of hydralazine and metoprolol in doses sufficiently high to keep the diastolic BP < 90 mmHg; the maximum doses are given in Table 1. In all but one patient (No. 1) the blood pressure was normal 6 to 8 weeks after delivery. A single oral dose of metoprolol 100 mg was again given 12–23 weeks after delivery. At this time all the women were still nursing their

Table 1. Clinical details of the subjects

Patient	1	2	3	4	5
No of previous pregnancies	II	0	I	0	0
No of previous deliveries	II	0	I	0	0
Smoking (cig/day)	0	0	0	0	≤10
Weight [kg][a]	68/63	63.5/55	73/62.5	65/55	100/91
Week[b]	29/15	35/23	33/21	33/12	34/22
Max. dose metoprolol	100 mg × 2	100 mg × 2	50 mg × 2	50 mg × 2	100 mg × 2
Max. dose hydralazine	75 mg × 2	75 mg × 2	50 mg × 2	50 mg × 2	75 mg × 2
Delivery at (completed weeks)	39	40	40	38	40
Birthweight [g] and sex of child	3880 (f)	3080 (m)	3570 (m)	3140 (m)	3520 (f)

[a] Patient's weight on study occasions
[b] First and second figure: number of completed weeks of pregnancy and number of weeks after delivery, respectively

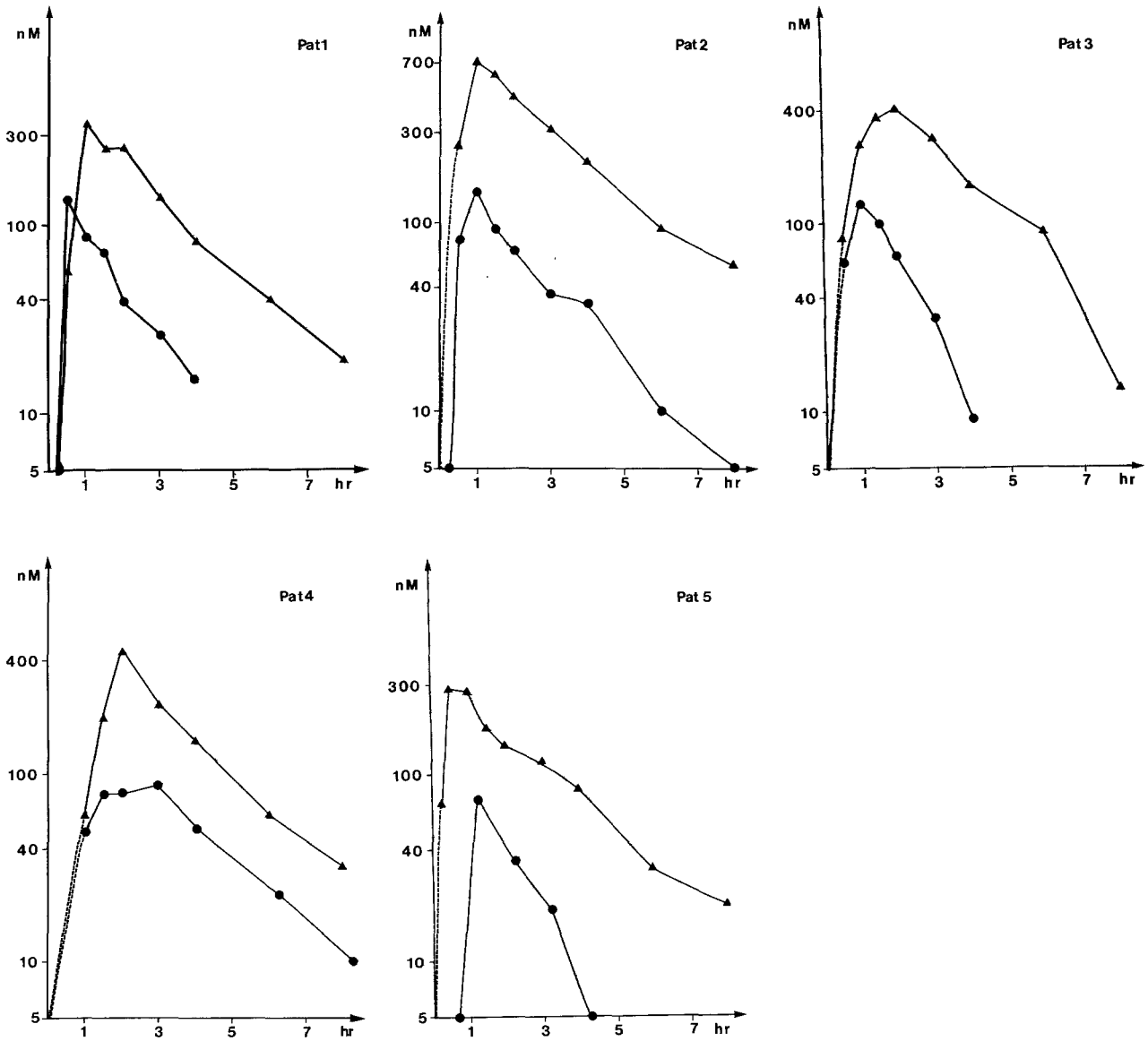

Fig. 1. Plasma concentration profiles after a single oral dose of metoprolol 100 mg in 5 women during the last trimester of pregnancy, and 12–23 weeks after parturition. The abscissa indicates the time [h] after dose. Triangles – concentration after pregnancy; filled circles – concentration during pregnancy

Table 2. Pharmacokinetics of metoprolol in the women

Patient no	Pregnant state					Non-pregnant state					
	β [l/h]	$t_{½}$ [h]	AUC tot [nmol/l × h]	Rest area of AUC [%]	Cl_o ml × kg^{-1} × min^{-1}	β [l/h]	$t_{½}$ [h]	AUC tot [nmol/l × h]	Rest area of AUC [%]	Cl_o [ml × kg^{-1} × min^{-1}]	$\frac{Cl_o\ (non\text{-}pregn)}{Cl_o\ (pregn)} \times 100$
1	0.478	1.45	226	14	407	0.417	1.66	920	5	108	26.5
2	0.452	1.53	337	3	292	0.351	1.98	2.163	7	53	18.0
3	0.919	0.75	240	5	357	0.584	1.19	1.405	2	71	19.9
4	0.380	1.82	382	7	251	0.400	1.73	1.167	6	97	38.8
5	0.865	0.80	124	6	502	0.352	1.97	834	6	82	16.3
$\bar{X}$	0.619	1.27	262	7	362	0.421	1.70	1.298	5	82	22.7

children. All the infants were healthy as judged by routine clinical examination.

On the study day metoprolol 100 mg was given in the morning after an over-night fast. Two h after the dose the patient received a standardized breakfast. Blood samples were collected through an indwelling catheter before and 15, 30, 60, 90, 120, 180, 240, 360 and 480 min after the dose. The blood was centrifuged more than 10 min but less than 60 min after collection, and the separated plasma was frozen at −20 °C until analysed by gas liquid chromatography (Ervik 1975).

Calculations

The elimination rate constant and the half-life of the terminal phase of the plasma concentration versus time curves were calculated by linear regression analysis of the terminal slope

$$t_{½} = \frac{0.693}{\beta} \quad (1)$$

The area under the plasma concentration versus time curve (AUC) was calculated by the trapezoidal rule. The residual area was calculated as C/β, where C is the plasma concentration at the last sampling time.

The apparent oral clearance, Cl_o was calculated as

$$Cl_o = \frac{Dose}{AUC} \quad (2)$$

Results

None of the patients experienced any adverse effect of the single oral dose or maintenance treatment with metoprolol. Peak plasma concentrations were achieved 1 to 2 h after administration (Fig. 1). In all women the peak concentration after pregnancy exceeded that observed during pregnancy by a factor of 2.5–5. Consistent with this observation, the value of the AUC was 3–6.7 times higher after pregnancy than during it (Table 2).

There was no systematic difference between the plasma half-lives during and after pregnancy, with the possible exception of Patient No. 5.

The apparent oral clearance (Cl_o) of metoprolol varied between 251 and 502 (ml × kg^{-1} × min^{-1}) in the pregnant women. After pregnancy, the apparent Cl_o was only 16–39% of the value obtained during pregnancy (Table 2).

Discussion

The high apparent oral clearance of metoprolol *during* as compared to *after* pregnancy has not previously been demonstrated for β-blocking agents. The finding is consonant with the observation of a comparatively low plasma steady-state concentration of phenytoin in pregnancy (Dam et al. 1979; Lander et al. 1977; Landon et al. 1979). Both of these drugs are almost entirely eliminated by metabolism.

It is believed that metoprolol is metabolized almost completely by the liver. As a result of the high apparent Cl_o in the pregnant state, peak concentrations of metoprolol were considerably lower than after pregnancy. The times to maximum plasma concentration were similar on the 2 study occasions and were similar to values previously reported in healthy volunteers (Johnsson and Regårdh 1976). One plausible explanation for the increased oral clearance in pregnancy is an increase in the microsomal monooxygenase enzyme system which catalyzes the oxidation of metoprolol (Arfwidsson et al. 1976).

The systemic clearance of high clearance drugs such as metoprolol is largely dependent on the hepatic blood flow (Wilkinson and Shand 1975). Blood flow changes could theoretically affect the half-life

of metoprolol, even after oral administration, but similar values were obtained during and after pregnancy. This is consistent with the view that pregnancy has a minor influence on hepatic blood flow in man (Krauer and Krauer 1977).

Theoretically, the present findings could also be explained by a lower degree of absorption of metoprolol during pregnancy. This possibility could not be studied with the present experimental design, but it seems unlikely in view of the equally rapid appearance of the peak concentrations on both occasions. Although intestinal motility decreases in pregnancy (Krauer and Krauer 1977), such a change would affect the rate rather than the degree of absorption.

The plasma protein binding of phenytoin, sulfisoxazole and salicylate (Crawford and Hooi 1968; Dean et al. 1980; Levy et al. 1975) is known to be lower than normal in pregnancy. This has also been shown for basic drugs, such as diazepam, propranolol and lidocaine (Wood and Wood 1981; Dean et al. 1980). The plasma protein binding of metoprolol is only about 12% (Johnsson and Regårdh 1976), so it appears unlikely that alteration in protein binding during pregnancy would exert any appreciable effect on the total plasma concentration.

In view of the large volume of distribution of metoprolol, the findings cannot be explained by the increase in plasma volume which occurs in pregnancy.

According to theory, the AUC after an oral dose of a drug which is completely absorbed and subject only to hepatic elimination, is solely determined by the intrinsic hepatic metabolic clearance and the plasma protein binding (Wilkinson and Shand 1975). Since metoprolol fulfils these criteria, increased hepatic metabolism in the pregnant woman seems to be the most likely explanation for the present findings.

It is conceivable that the effect and side-effects of metoprolol would be lower per dose or unit plasma concentration in the pregnant than in the non-pregnant woman. This might have clinical relevance in patients treated only with a β-blocker. No study of the metoprolol dose-effect relationship in hypertension in pregnant women appears to have been published.

In Sweden it is a therapeutic tradition to combine metoprolol with hydralazine in hypertensive pregnant women. This makes it difficult to determine whether a higher dose of metoprolol would be required to control blood pressure in pregnancy.

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