Atenolol Developmental Toxicity: Animal-to-Human Comparisons

Sonia Tabacova,[1]* Carole A. Kimmel,[2] Kelly Wall,[3] and Deborah Hansen[3]

[1]Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, Maryland
[2]National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC
[3]National Center for Toxicological Research, US Food and Drug Administration, Jefferson, Arkansas

Received 9 July 2002; Revised 7 November 2002; Accepted 11 November 2002

BACKGROUND: Atenolol, 4-2′-hydroxy-3′-isopropyl-aminopropoxy) phenylacetamide, is a beta-adrenoreceptor blocker used for treatment of hypertension in pregnancy. Beta-blockers are reported to cause fetal harm (such as decreased birth weight) when administered to a pregnant woman. We evaluate published human and animal evidence of atenolol developmental toxicity and compare the manifestations in humans and in routinely-used animal models. **METHODS:** The comparison is based on the following criteria: comparability of pharmacokinetic/pharmacodynamic characteristics, type of adverse outcome, lowest adverse effect levels, and specificity and selectivity of effect. **RESULTS:** Manifestations of atenolol prenatal toxicity (placental changes, intrauterine growth retardation and changes in fetal weight in the absence of structural malformations) are similar in the tested animal species (rats and rabbits) and humans. The human seems to be more sensitive, however, because adverse embryo-fetal effects are reported at doses much lower than those in the tested species. In humans and rats, adverse embryo-fetal effects are induced by doses that are not maternally toxic. In the rabbit, however, such effects are seen only at maternally toxic doses, suggesting that in this species, developmental toxicity may be maternally mediated. **CONCLUSIONS:** The available data suggest animal–human concordance with regard to the nature and manifestations of atenolol prenatal toxicity. The animal models "predicted" developmental toxicity manifests as placental changes, intrauterine growth retardation and fetal weight decrease in the absence of structural malformations. Thus far, this is concordant with the data from humans, in whom intrauterine growth retardation has been observed but not structural abnormalities. *Birth Defects Research (Part A) 67:181–192, 2003.*

INTRODUCTION

Atenolol, (4-2′-hydroxy-3′-isopropyl-aminopropoxy) phenylacetamide, is an antihypertensive, cardioselective beta-adrenoreceptor blocker used in pregnancy to treat pre-existing or pregnancy-associated hypertensive disorders. These conditions are among the most frequent complications of pregnancy (Report of the National High Blood Pressure Education Program, 2000). It is recognized that beta-blockers, including atenolol, can cause fetal harm, such as decreased birth weight, when administered to a pregnant woman (Physician's Desk Reference, 2001). Clinical studies and surveys of atenolol-treated pregnant patients conducted since its approval in 1981 have contributed to an increasing body of information on adverse developmental effects of atenolol in human subjects. We evaluate published human and animal evidence of atenolol developmental toxicity and compare manifestations in humans and in experimental animals, with the aim of assessing the predictability of standard testing approaches in animal studies for the human.

MATERIALS AND METHODS

Human Studies

The available information on outcomes of gestational exposures to atenolol in humans, published since 1982, comprises 22 primary publications including group-level studies (clinical trials, surveys, and case series) and individual case reports. The present evaluation is based on the group-level studies (19 articles). These articles are based on 12 studies (Table 1), some of which have been published in more than one article. The majority of these studies (8/12) are clinical trials, three are surveys, and one is a small case series. Altogether, these studies encompass 1083 women with hypertensive complications of pregnancy. Of these, 458 were treated with atenolol at different times during gestation, and the rest were either untreated, treated with placebo or treated with other antihypertensive drugs for comparison.

Animal Studies

For comparison to human studies, only reproductive and developmental toxicity studies conducted in mamma-

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*Correspondence to: Sonia Tabacova, FDA, NDPDP, 5600 Fishers Lane, HFD-120 Rockville, MD 20857. E-mail: tabacovas@cder.fda.gov
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.10011

Table 1
Reviewed Studies in Humans

Study design	*n* subjects total (Atenolol-treated)	Atenolol dose oral (mg/day)	Time of exposure (trimester of pregnancy)	Indication for treatment	Reference
Clinical trials					
Placebo-controlled					
Prospective, double-blind, randomized	120 (46)	100	3rd	Pregnancy-induced hypertension (PIH)	Rubin et al. (1983, 1984); Reynolds et al. (1984)
Prospective, double-blind, randomized	29 (15)	50–200	2nd, 3rd	Essential hypertension	Butters et al. (1990)
Prospective, double-blind, randomized	74 (28)	100	2nd, 3rd	Hemodynamic abnormalities; risk of pre-eclampsia	Easterling et al. (1999)
Non-placebo-controlled					
Prospective non-randomized[a]	56 (28)	100–200	2nd, 3rd	PIH (89%) Pre-existing hypertension (11%)	Lardoux et al. (1983)
Prospective non-randomized[a]	51 (24)	50–100	2nd, 3rd	PIH, Pre-eclampsia	Tiumala and Hartikainen (1988)
Prospective randomized[a]	50 (25)	100–150	3rd	PIH	Marlettini et al. (1990)
Prospective double-blind, randomized[a]	29 (13)	50	3rd	PIH	Montan et al. (1992)
Prospective randomized recruitment[b]	70 (70)	50–150	2nd, 3rd	PIH (74%) Pre-eclampsia (9%) Chronic hypertension (17%)	Fabregues et al. (1992)
Surveys					
Prospective[a]	121 (31)	100–200	1st, 2nd, 3rd	Chronic hypertension, PIH	Dubois et al. (1982, 1983)
Retrospective	119 (97)	50–200	1st, 2nd, 3rd	PIH (90%) Pre-existing hypertension (10%)	Liedholm (1983)
Prospective[c]	359 (76)	Therapeutic (Not specified)	1st, 2nd	Chronic hypertension	Lip et al. (1997)
Case series	5 (5)	50–100	1st, 2nd, 3rd	Chronic hypertension	Crichton et al. (1996)

[a]Comparisons made with groups treated with other antihypertensive drugs.
[b]Comparisons made across groups with different indications for atenolol treatment.
[c]Comparisons made with untreated patients.

lian species in vivo were taken into account. Such studies have been carried out in rodents and in the rabbit (Table 2). The rodent studies include two reproductive/fertility studies in the rat, with maternal and paternal pre-mating atenolol treatment followed by maternal treatment either through the first week of gestation, or throughout the entire pregnancy and lactation (up to postnatal day 21); a teratology study with exposure during organogenesis (gestational day [g.d.] 6–15); and two studies on postnatal functional and neurobehavioral development of the progeny after maternal treatment either throughout gestation or during late pregnancy. In addition to the latter studies that followed the development of rat progeny up to maturity, some postnatal assessments (viability and weight gain) during the pre-weaning period were carried out in the teratology study and one of the fertility studies. The two available rabbit studies involved only prenatal assessments after maternal atenolol treatment either during organogenesis (g.d. 6–18), or from g.d. 7–25 (normal gestational period is 28–30 days).

Animal–Human Concordance

The assessment of animal–human concordance in the developmental effects of prenatal atenolol exposure was based on the following criteria:

- Comparability of atenolol pharmacokinetic/dynamic characteristics in animals and humans;
- Presence of any adverse developmental effect in animals and in human subjects;
- Comparability of the type of effect by category of outcome (e.g., intrauterine death, abnormal intrauterine growth or morphological differentiation, postnatal developmental disturbances);
- Comparability of the dose levels inducing developmental effects;
- Selectivity of effect (e.g., embryo-specific or mediated through maternal toxicity);
- Specificity of effect with regard to the agent's pharmacodynamics.

Table 2
Reviewed Studies in Experimental Animals

Study type	Species, strain	Atenolol dose range, (mg/kg/day)	Time and duration of maternal exposure[a]	Route of administration	Reference
Reproductive/fertility evaluation					
	Rat, Sprague Dawley	6.4–100	2 weeks prior to mating through gestation and lactation	oral	Fitzgerald (1979)
	Rat, unspecified	20–2000	2 weeks prior to mating through G. day 7	oral	Esaki and Imai (1980)
Developmental prenatal evaluation					
	Rat, Wistar	25–200	G. Day 6–15	oral	Fitzgerald (1979)
	Rabbit, New Zealand	5–25	G. Day 6–18	oral	Fitzgerald (1979)
	Rabbit, New Zealand	1.0	G. Day 7–25	Intraperitoneal	Katz et al. (1987)
Developmental postnatal evaluation					
	Rat, Wistar	5–20	G. day 1–birth	oral	Ryan and Pappas (1990)
	Rat, Wistar	7.5–15	G. day 8–22	oral	Speiser et al. (1991)

[a]G. day, gestational day.

Assessment of animal–human pharmacokinetic/dynamic comparability was made before comparing the manifestations of atenolol developmental toxicity (Tabacova and Kimmel, 2002). The available experimental and human studies were reviewed and evaluated separately for reliability.

Evaluation of Human Studies

The evaluation of the human studies followed a series of consecutive steps. The first step involved data abstraction to describe study characteristics, exposure parameters (dose, time, and duration of atenolol treatment), other potential risk factors, adverse developmental outcomes (embryo-fetal death, congenital anomalies, altered birth weight, preterm birth, early postnatal complications, postnatal developmental, and neurobehavioral or other organ system deviations) and maternal effects.

The second step was the evaluation of each study for data reliability and involved the following criteria: reliability of study design; appropriate control group; number of subjects; adequate assessment of exposure and outcome(s); control of potential confounding factors (e.g., maternal age, reproductive history, concurrent disease, concomitant medication, socioeconomic factors); and relevant analysis to assess the relation between exposure and outcome(s).

Assessment of the evidence for association between the reported adverse effects and atenolol exposure was the final step in the evaluation human studies. This assessment was based on the following criteria (Hill, 1965): strength of evidence; consistency of evidence; specificity of effect; temporality of effect; dose–dependence of effect; plausibility of effect; and coherence with existing knowledge.

Based on this assessment, a selection of outcomes likely to be associated with atenolol gestational exposure in humans was made for comparison with experimental animal data.

Evaluation of Animal Studies

The review and evaluation of experimental animal studies were conducted following a sequence of procedures similar to that used in the evaluation of human studies. As in the human studies evaluation, the first step involved data abstraction using a uniform format to facilitate comparison across studies. The format was based, in general, on that used in the National Toxicology Program Special Reproductive Study (Chapin and Sloane, 1997) and included endpoints describing study particulars, exposure parameters, effect characteristics, dose–time effect relationship, as well as possible confounding factors. All outcomes pertaining to the categories of embryo-fetal death, intrauterine growth, structural abnormalities, postnatal viability and physical, functional, and neurobehavioral development, as well as maternal condition, were taken into account.

The second step involved the evaluation of animal studies with regard to their reliability for extrapolating the data to humans. The evaluation was carried out according to the following criteria: adequacy of the experimental model; adequacy of the dose and route of administration; adequacy of the timing and duration of exposure; sufficient number of animals per group; presence of a dose–effect relationship; appropriate statistical analysis; and confounding and interfering factors that may have compromised the validity of the study conclusions.

The final step was the evaluation of reported adverse outcomes (by category) with regard to their causal relationship to atenolol exposure. The criteria included statistical significance of effect; dose–dependence of effect; consistency of effect across studies; consistency of effect across species; influence of confounding and interfering factors; and plausibility of effect with regard to pharmacokinetic and pharmacodynamic properties of the agent.

RESULTS AND DISCUSSION

Human Studies

Evaluation of studies. Of the 12 studies reviewed, 5 were randomized, double blind, controlled clinical trials; 3 were nonrandomized clinical trials that had no untreated (or placebo-treated) control groups; 3 were surveys, and 1 was a small case series. Except for one of the surveys, all studies had a prospective design. The data collection was based on direct observation. Only one study (Liedholm, 1983) abstracted the data retrospectively from medical records. Reference groups were included in 9 of 12 studies (Table 1), but only 4 of these actually involved nonexposed (untreated or placebo-treated) control subjects; the rest had reference groups treated with other antihypertensive drugs. In the majority of studies (9/12), the sample size was over 50 patients (Table 1).

All studies provided adequate information about the dose and timing of atenolol exposure; atenolol was administered invariably for therapeutic purposes. The prevailing indication for treatment was pregnancy-induced hypertension (8/12 studies). Other indications were preexisting chronic or essential hypertension in three studies and, in one study, hemodynamic abnormalities in patients at risk of preeclampsia before development of hypertension (Easterling et al., 1999). All doses were within the therapeutic dose range; the daily doses varied from 50 to 200 mg orally. Most studies (10/12) involved (exclusively or predominantly) exposures during the 2nd and 3rd trimesters of pregnancy. The duration of treatment ranged from 1 week to the entire pregnancy. Thus, although the dose and the timing of exposure were essentially uniform, the exposure duration varied widely among and within studies. Because all doses were in the therapeutic dose range, the data did not lend themselves to assessment of a dose–effect or dose–response relationship. Only one study (Fabregues et al., 1992) attempted a dose–effect comparison among three atenolol dose groups (mean group dose levels 62, 70, and 100 mg/day), but no intergroup differences in the outcomes were found, presumably because of the narrow dose range and the small numbers of subjects in the subgroups.

All studies provided data on the main categories of adverse prenatal developmental outcomes (embryo-fetal death, restricted growth, and congenital abnormalities). The prospective design of most of the reviewed studies minimized the risk of a recall bias; however, most studies lacked data on postnatal development beyond the first week of life.

Statistical analysis of the association between exposure to atenolol and adverse outcomes was carried out in all but two studies: a retrospective survey (Liedholm, 1983), and a case series (Crichton, 1996). The association was analyzed by a comparison of atenolol-treated with either untreated or non–atenolol-treated groups.

Other possible risk factors and confounding factors were considered in all but two studies (Liedholm, 1983; Crichton, 1996). Maternal age, reproductive history, background maternal disease, and concomitant drug use were recorded in 10 of 12 reviewed studies; however, socioeconomic and lifestyle factors were often disregarded. Such factors could have been important because intrauterine growth retardation was one of the most frequently reported adverse outcomes, and it is common knowledge that maternal nutrition and socioeconomic status have an influence on fetal growth and weight at birth. Although the role of possible confounding factors was discussed in most of the studies, it was analyzed statistically (regression analysis) in only one study (Lip et al., 1997).

In summary, considering all study characteristics discussed above, the overall reliability of the reviewed 12 studies was evaluated as good in five and limited in seven studies. The studies considered to have good reliability (Reynolds et al., 1984; Rubin et al., 1984; Butters et al., 1990; Marlettini et al., 1990; Lip et al., 1997, Easterling et al., 1999) accounted for over 50% of the total number of subjects included in all studies (632/1083 patients).

Evaluation of outcomes in humans. Table 3 summarizes the reported outcomes by category and the evaluation with regard to the association with maternal atenolol exposure (see Materials and Methods).

The majority of the reviewed studies concentrated on prenatal and perinatal adverse events, whereas postnatal outcomes beyond the first week of life were followed in few studies. The available information was insufficient to allow assessment of atenolol effects on the postnatal physical and neurobehavioral development.

The most consistently reported prenatal adverse events were reduced placental weight, decreased birth weight, and intrauterine growth retardation (IUGR). Such outcomes were found in all or most of the publications that studied these endpoints. One of the most pronounced adverse outcomes was placental weight reduction, found in all of five studies that measured placental weight. In some of these studies, tests for placental functional assessment were carried out. The tests provided evidence for a significantly decreased production of placental lactogen, which is a polypeptide used as an indicator of placental function (Rubin et al., 1983, 1984; Tiumala and Hartikainen-Sorri, 1988). IUGR and decreased birth weight (relative to gestational age) were found in 6 and 8 studies, respectively, of 11 studies that provided data on these outcomes. Such adverse events could have resulted from the maternal hypertension per se that was the indication for atenolol treatment. However, these disturbances were also apparent in atenolol-treated versus non–atenolol-treated groups of hypertensive patients (Dubois et al., 1982, 1983; Lardoux et al., 1983; Tiumala and Hartikainen-Sorri, 1988; Butters et al., 1990; Marlettini, 1990; Lip et al., 1997), as well as in atenolol-treated nonhypertensive patients (Easterling et al., 1999). Thus it is reasonable to assume that the agent, rather than the maternal hypertension, was responsible. The most likely reasons for these effects were placental and fetal hemodynamic disturbances associated with atenolol pharmacodynamic effect. The studies that measured maternal/fetal hemodynamic parameters (Montan et al., 1992; Crichton, 1996), showed a significant reduction in umbilical and fetal aortic blood flow, with or without reduced fetal heart rate. The increased resistance to blood flow in the fetoplacental circulation has been attributed to the lack of an intrinsic sympathomimetic (vasodilating) effect of atenolol, rather than to a decrease in fetal heart rate (Loquet et al., 1988).

The outcomes listed above are likely to be associated with atenolol exposure because they are in compliance with Hill's criteria for establishing causality (Hill, 1965); that is, strength of evidence (in the majority of studies, changes were statistically significant compared to reference groups with similar maternal background diseases); consistency of evidence (confirmed, for different outcomes,

Table 3
Evaluation of Adverse Pregnancy Outcomes Reported in Human Studies

			Criteria for relationship to atenolol exposure[a]							
Outcomes	Observed effect	Ref.[b]	Consistency of evidence (*n* confirmatory studies per *n* studies with information available)	Strength of evidence (Effect statistically significant in *n* studies per *n* confirmatory studies)	Reliability of data source(s)	Specificity of effect	Temporality of effect	Reversibility of effect if exposure is discontinued	Dose-effect dependence	Plausibility of finding
Spontaneous abortion	No effect	1,3,4,6,10,11	(+) (6 of 6)[c]	NA (no effect)	(+)	NA (no effect)	NA (no effect)	NA	NA (no effect)	(+)
Stillbirth	Uncertain	3,4,6	(−) (3 of 11)[d]	(−)	(+)	(−)	(+)	NA	ND	(+)
Altered birth weight	Decrease	1,3–7,10–12	(+) (9 of 11)[d]	(+) (7 of 8)	(+)	(−)	(+)	ND	ND	(+)
Congenital anomalies	No effect	1–12	(+) (12 of 12)	NA (no effect)	(+)	NA (no effect)	NA (no effect)	NA	NA (no effect)	(+)
IUGR	Increase	1,4,6,7,10,11	(+) (6 of 11)[d]	(+) (5 of 6)	(+)	(−)	(+)	ND	ND	(+)
Altered placental weight	Decrease	2,5,6,8,10	(+) (5 of 5)	(+) (3 of 5)	(+)	(−)	(+)	ND	ND	(+)
Peri/postnatal complications										
Bradycardia (fetal/neonatal)	Increase	2,7,8	(±) (3 of 6)	(+) (3 of 3)	(±)	(+)	(+)	(+)	ND	(+)
Hypoglycemia	Increase	3,4,12	(−) (3 of 8)	(−) (0 of 3)	(−)	(±)	(+)	(+)	ND	(+)
Arterial hypotension	No effect	2,4,5,7	(+) (4 of 4)	NA (no effect)	(±)	NA (no effect)	NA (no effect)	NA (no effect)	NA (no effect)	(?)
Respiratory	No effect	2–5,7–9	(+) (6 of 7)	NA (no effect)	(+)	NA (no effect)	NA (no effect)	NA (no effect)	NA (no effect)	(+)
Growth and physical development	No effect	2,6	(+) (2 of 2)	NA (no effect)	(±)	NA (no effect)	NA (no effect)	NA (no effect)	NA (no effect)	(?)
Neurobehavioral deviations	No effect	2	(?) (1 of 1)	NA (no effect)	(±)	NA (no effect)	NA (no effect)	NA (no effect)	NA (no effect)	(?)
Infant mortality	No effect	1–9	(+) (9 of 9)	NA (no effect)	(+)	NA (no effect)	NA (no effect)	NA (no effect)	NA (no effect)	(+)

Symbols used: (+), criterion met; (−), criterion unmet; (±), criterion partially met; (?), unable to assess; ND, no data; NA, not applicable.

[a]Description of criteria: Consistency of evidence: (+), data consistent; (−), data inconsistent (*n* confirmatory studies for presence (or absence) of effect per *n* studies with information on a given endpoint available). Strength of evidence: (+), the observed effect is statistically significant; (−), statistically non-significant. Reliability of data sources: (+), out of all studies with information on a given endpoint, at least 3 are controlled epidemiological studies; (±), less than 3; (−), no controlled epidemiological studies. Specificity of effect: (+), the observed effect is specific for the agent; (−), the observed effect is not specific for the agent. Temporality of effect: (+), the exposure to the suspect agent has taken place prior to the reported outcome. Plausibility of effect: (+), the finding is plausible having in mind the pharmacokinetic/dynamic properties of the agent.

[b]References: 1. Dubois et al. (1982, 1983); 2. Rubin et al. (1983, 1984), Reynolds et al. (1984); 3. Liedholm (1983); 4. Lardoux et al. (1983); 5. Tiumala, Hartikainen-Sorri (1988); 6. Butters et al. (1990); 7. Marlettini et al. (1990); 8. Montan et al. (1992); 9. Fabregues et al. (1992); 10. Lip et al. (1997); 11. Chrichton (1996); 12. Easterling et al. (1999).

[c]*n* studies involving 1st and 2nd trimester exposures.

[d]Excluding one study (Fabregues et al., 1992) that compared only atenolol-treated patients (no reference group).

Table 4
Outcomes of Prenatal Atenolol Exposure in Experimental Animal Studies

Outcomes	Species	Observed effect (vs. control)	*n* studies reporting this finding per total *n* studies on respective endpoint (*n*)	Effect found at exposure during: (*n* studies per *n* performed)		LOAEL (mg/kg/d oral, unless otherwise specified)
				Organogenesis through birth	Premating+ throughout gestation	
1	2	3	4	5	6	7
Prenatal						
Embryo/fetal loss	Rat	↑ Increase	1/3	1/1	0/2	50
	Rabbit	↑ Increase	1/1	1/1	ND	25
Litter size	Rat	↓ Decrease	1/3	1/1	0/2	200
	Rabbit	No effect	1/1	0/1	ND	—
Fetal weight	Rat	↓ Decrease	1/2	ND	1/2	200
	Rabbit	No effect	1/1	0/1	ND	—
Placental weight	Rat	↓ Decrease	1/1	1/1	ND	25
	Rabbit	↑ Increase	1/1	1/1	ND	1 (i.p.)
Malformations	Rat	No effect	3/3	0/1	0/2	—
	Rabbit	No effect	2/2	0/2	ND	—
Variations and deviations	Rat	↑ Increase[c]	2/3	1/1	1/2	50 or 20
	Rabbit	↑ Increase[d]	1/2	1/2	ND	1 (i.p.)
Postnatal						
Live born litter size	Rat	↓ Decrease	1/4	1/2	0/2	200
	Rabbit	↓ Decrease	1/1	1/1	ND	1 (i.p.)
Stillbirths	Rat	No effect	4/4	0/2	0/2	—
Birth weight	Rat	↓ Decrease	1/4	1/2	0/2	100
	Rabbit	↓ Decrease	1/1	1/1	ND	1 (i.p.)
Heart Rate	Rat	Bradycardia (1st day of life)	1/1	1/1	ND	7.5
Postnatal weight and weight gain	Rat	↓ (pre-weaning)	1/3	0/2	1/1	100
		↓ (maturity, males only)	1/1	ND	1/1	5
Developmental landmarks	Rat	No effect	2/2	1/1	1/1	—
Neurobehavioral development	Rat	Delayed conditioned avoidance response	1/2	1/1	0/1	7.5
Postnatal survival	Rat	↓ Decrease (up to weaning)	1/3	1/2	0/1	200
Maternal toxicity						
Weight	Rat	No effect	3/3	0/1	0/2	—
	Rabbit	↓ Decrease	1/2	1/2	ND	10
Clinical signs	Rat	No effect	3/3	0/1	0/2	—
	Rabbit	Present	1/2	1/2	ND	25
Mortality	Rat	No effect	3/3	0/1	0/2	—
	Rabbit	↑ Increase	1/2	1/2	ND	25

in 60–100% of studies that had information on the respective endpoints); temporal association with atenolol exposure; and plausibility with regard to the pharmacodynamic effect of atenolol on fetal and utero–placental circulation.

No increases in embryo-fetal death or congenital abnormalities were reported in association with atenolol treatment. Stillbirths were reported sporadically (in 3/11 studies that provided information on this endpoint). One of these three studies was a retrospective survey of all hypertensive pregnancies in Sweden that compared the prevalence of stillbirths in the survey with the background rate for the entire country population (Liedholm, 1983). Such a comparison is flawed because it does not take into account the maternal hypertension, which by itself is a risk factor for intrauterine fetal loss (Redman, 1982). In another study, the only stillbirth observed among atenolol-treated pregnancies occurred in a patient with placental abruption and cocaine intoxication (Easterling et al., 1999). The third

NOAEL (mg/kg/d oral, unless otherwise specified)	Dose range tested (mg/kg/d)	Effect statistically significant	Effect dose-dependent	Plausibility of finding[a]	Consistency of finding[b]	References[e]
8	9	10	11	12	13	14
25	25–200	(+)	(+)	(?)	(−)	1, 2
10	5–25	(−)	(+)	(+)	NSD	1
50	25–200	(−)	(+)	(+)	(−)	1, 2
25	5–25	NA	NA (no effect)	(?)	NSD	1
20	20–200	(+)	(+)	(+)	NSD	1, 2
25	5–25	NA	NA (no effect)	(?)	NSD	1
—	25–200	(+)	(+)	(+)	NSD	1
—	1 (i.p.)	(+)	NA (one dose)	(+)	NSD	3
200	20–200	NA	NA (no effect)	(+)	(+)	1, 2
25; 1 (i.p)	5–25; 1 i.p	NA	NA (no effect)	(+)	NSD	1, 3
10	20–200	(+)	(+)	(+)	(+)	1, 2
—	1 (i.p.)	(+)	NA (one dose)	(+)	NSD	1, 3
50	5–200	(−)	(+)	(+)	(+)	1, 4, 5
—	1 (i.p.)	(−)	NA (one dose)	(+)	NSD	3
200	5–200	NA	NA (no effect)	(?)	(+)	1, 4, 5
40	5–200	(−)	(+)	(+)	(−)	1, 4, 5
—	1 (i.p.)	(−)	NA (one dose)	(+)	NSD	3
—	7.5	(+)	NA (one dose)	(+)	NSD	4
40	6.4–100	(−)	(+)	(+)	(−)	1
—	5–20	(+)	(−)	(+)	(−)	5
20	5–20	NA	NA (no effect)	(+)	(+)	4, 5
—	7.5	(+)	NA (one dose)	(?)	(−)	4, 5
50	25–200	(−)	(+)	(+)	(+)[†]	1, 4
2000	20–2000	NA	NA (no effect)	(+)	(+)	1, 2
5; 1 (i.p)	5–25; 1 i.p	ND	(+)	(+)	NSD	1, 3
2000	20–2000	NA	NA (no effect)	(+)	(+)	1, 2
10; 1 (i.p.)	5–25; 1 i.p	ND	(+)	(+)	NSD	1, 3
2000	20–2000	NA	NA (no effect)	(+)	(+)	1, 2
10; 1 (i.p.)	5–25; 1 i.p	ND	(+)	(?)	NSD	1, 3

[a]Plausibility: the finding is plausible with regard to the pharmacokinetic/dynamic characteristics of the agent.
[b]Consistency: the finding is consistent across studies.
[c]Renal pelvic enlargement (Fitzgredrald, (1979) and pronounced retardation in skeletal ossification (Esaki and Imai, 1980).
[d]Decreased umbilical cord length (Katz et al. (1987).
[e]References: 1. Fitzgerald (1979) (NDA). 2. Ezaki and Imai (1980). 3. Katz et al. (1987). 4. Speiser et al. (1991). 5. Ryan and Pappas (1990).
LOAEL, lowest adverse effect level; NOAEL, no adverse effect level; (+), criterion met; (−), criterion unmet; (±), criterion partially met; (?), unable to assess; ND, no data; NSD, insufficient data (small number of studies or subjects within studies); NA, not applicable; —, LOAEL or NOAEL outside the tested dose range; i.p., interperitoneal.

study that reported stillbirths was a clinical trial with a small number of subjects (n = 28) and no untreated reference group (Lardoux et al., 1983).

Bradycardia and hypoglycemia have been observed in the perinatal and early postnatal period. Of the studies that measured these endpoints, bradycardia was found in three of six studies and hypoglycemia in three of eight studies. These effects were reversible after exposure to atenolol was discontinued.

The prevalence of perinatal bradycardia among atenolol-treated pregnancies was significantly higher than in reference groups in each of three studies that reported this effect (all of them prospective, random, double blind clinical trials). One of these studies found a pronounced increase in the occurrence of infant bradycardia in the early neonatal period after maternal treatment with atenolol versus placebo (Rubin et al., 1983, 1984). Two other studies (Marlettini et al., 1990; Montan et al., 1992) found a signif-

icantly higher proportion of fetal bradycardia, but it was no longer observed after birth. These studies were not placebo-controlled and compared atenolol-treated groups with groups treated with other antihypertensive drugs.

A nonsignificant increase in the rate of neonatal hypoglycemia was reported in two studies (Lardoux et al., 1983; Liedholm, 1983). In another study, conducted among patients at risk of preeclampsia (nulliparous and diabetic), neonatal hypoglycemia occurred at a similar rate in atenolol-treated non-diabetic mothers and in non–atenolol-treated diabetics (Easterling et al., 1999).

Neonatal arterial hypotension and renal disorders were not reported in any of the reviewed studies. No increase in infant death rate was observed.

Postnatal development beyond the early neonatal period was followed in only two studies (Rubin et al., 1983; Butters et al., 1990), both reliable with regard to the study design (prospective, randomized, double blind, placebo-controlled clinical trials). No deviations in physical development (weight, length, occipito-frontal head circumference, triceps and subscapular thickness) or neurobehavioral parameters (Denver developmental screening test) were found at 3, 6, and 12 months of life. These findings are supported by a follow-up study of 104 infants of mothers treated with unspecified beta-blockers in comparison to an equal number of control infants of similar gestational age and birth weight, but without pregnancy complications (Svenningsen et al., 1984). At 2 years of age, the rate of neurobehavioral handicaps was similar in the study population and in the control infants. Thus, although insufficient, the available information points to an absence of adverse effects after prenatal atenolol exposure on postnatal physical or neurobehavioral development.

Animal Studies

Evaluation of studies. All reviewed studies (Table 2) were carried out in vivo, in protocols using mammalian species employed routinely for standard developmental toxicity testing.

In all but one study, atenolol was administered orally, by gavage (corresponding to the route of human exposure), at daily doses in the range of 5–2000 mg/kg in the rat, and 5–25 mg/kg in the rabbit. At the lower end of this range, the doses were close to the human oral therapeutic dose range of 0.7–3 mg/kg/day. A different route (intraperitoneal) was used in only one study (rabbit), at a dose of 1 mg/kg per day (Katz et al., 1987). Human daily oral dose on a milligram per kilogram basis. Most studies employed multiple dose levels that allowed assessment of dose–effect and dose–response relationships. Two studies (one in each species tested) employed only one atenolol dose level similar to the human therapeutic dose (Katz et al., 1987; Speiser et al., 1991).

The timing of exposure was limited to the period of major organogenesis in two studies; the rest employed longer periods of treatment, starting either before mating or after implantation and continuing through pregnancy (Table 2). It should be noted that in humans, the timing of atenolol exposure in pregnancy rarely involves the period of organogenesis (1st trimester) because the main indication for atenolol treatment is hypertensive complications, which usually develop after the 1st trimester.

The number of animals/litters tested per dose group was sufficient, with the exception of one study in the rabbit (Katz et al., 1987). In the studies involving postnatal assessments, progeny were culled to a specified number on postnatal day 1 or 4 to standardize the litter size.

Adverse developmental effects in experimental animals. The prenatal effects of maternal atenolol exposure were assessed in the rat (two strains) and rabbit, whereas postnatal assessments were carried out almost exclusively in the rat. In the rabbit, very limited perinatal assessments were available. In the single study that allowed the does to deliver spontaneously, the progeny were sacrificed at birth. A description and evaluation of the observed pre- and postnatal developmental effects are presented in Table 4.

Exposures limited to the period of major organogenesis (g.d. 6–15 and 6–18 in the rat and rabbit, respectively) produced signs of embryotoxicity in both species at oral doses at or above 25 mg/kg/day. This was expressed by a moderate increase in embryo-fetal death (resorptions) in both species and by reduced placental weight, retarded skeletal ossification, and visceral variations in the rat. In the rabbit, placental weight changes and a marked decrease in the umbilical cord length were observed with intraperitoneal maternal application of atenolol at a dose of 1 mg/kg per day. On a milligram per kilogram basis, this dose is in the range of the human oral therapeutic doses, even after taking into account the incomplete atenolol absorption (about 60% of the ingested dose). The lowest adverse effect level (LOAEL) for embryotoxicity with oral atenolol treatment seemed to be similar in the two tested species (about 25 mg/kg/day). It should be noted, however, that in the rabbit this dose produced maternal toxicity, whereas in the rat maternal toxicity was not induced even by doses more than one order of magnitude higher than those inducing developmental effects. This suggests that the observed embryotoxicity in the rabbit could have been secondary to maternal toxicity, whereas in the rat, the embryo-fetal effects were obviously not maternally-mediated.

With exposures continuing through pregnancy, a significant decrease in the heart rate of the offspring of atenolol-treated rats was found during the first 24 hr of life. This effect, attributable to the pharmacologic action of the drug (Speiser et al., 1991), was seen at lower dose levels (7.5 mg/kg/day) than those eliciting adverse developmental effects. No significant changes in birth weight, perinatal mortality, postnatal survival, or developmental milestones were observed in the progeny up to the highest tested atenolol doses (100 or 200 mg/kg in different experiments). Delayed developmental effects that are, however, not manifested until maturity, such as decreased weight gain of male offspring and neurobehavioral deviations (delayed acquisition of conditioned avoidance response), were reported in single studies. The LOAEL for these effects in the rat (5 and 7.5 mg/kg/day, respectively) were of the same order of magnitude as the human therapeutic dose (on a milligram per kilogram basis). Because of the very limited number of postnatal rat studies, however, the reproducibility of these observations cannot be assessed. No postnatal developmental studies have been carried out in the rabbit.

In summary (Table 5), the most sensitive endpoints of atenolol developmental toxicity in the tested animal species (rat and rabbit) were deviations in placental weight (both species), structural deviations indicative of sup-

Table 5
Atenolol Lowest Adverse Effect Levels for Developmental Outcomes in Two Animal Species

	Rat		Rabbit	
Endpoints	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)
Fetal heart rate	7.5	<7.5	ND	ND
Neurobehavioral deviations	7.5	<7.5	ND	ND
Structural variations	20	10	1 (i.p.)	<1 (i.p.)
Placental weight	25	<25	1 (i.p.)	<1 (i.p.)
Embryo-fetal loss	50	25	25	10
Fetal weight at term	100	40	>25	25
Postnatal weight gain	100	40	ND	ND
Postnatal survival	200	50	ND	ND
Congenital malformations	—	≥2000[a]	—	≥25[a]
Maternal toxicity	>2000	2000	10	5
			1 (i.p.)	<1 (i.p.)

Oral doses unless otherwise indicated.
[a]Highest dose tested.
LOAEL, lowest adverse effect level; NOAEL, no adverse effect level; ND, no data; i.p., interperitoneal.

pressed intrauterine growth (i.e., skeletal ossification delays) and postnatal neurobehavioral disturbances in the rat, suggestive of delayed cognitive development at maturity. These endpoints were affected at oral dose levels in the range of 5–20 mg/kg (rat), whereas the lowest adverse effect levels for other developmental endpoints in this species (i.e., embryo-fetal loss, fetal weight, and postnatal survival) were in the range of 50–200 mg/kg/day. In the rat, all these effects occurred at dose levels much lower than the LOAEL for maternal toxicity (>2000 mg/kg/day) suggesting that the observed effect is embryo-specific and not related to maternal toxicological changes. In contrast, signs of maternal toxicity in the rabbit were present down to the lowest doses producing embryo-fetal effects. Congenital malformations were not induced in either tested species, even by maternally toxic doses of atenolol.

Animal-to-Human Comparisons

Pharmacokinetic and pharmacodynamic aspects. The animal–human comparison of atenolol developmental toxicity is justified by the general similarity in disposition and mode of action of the drug in human subjects and animal species used routinely for developmental toxicity assessments (as reviewed in Tabacova and Kimmel, 2002). Such species (i.e., rats and rabbits) handle the drug in a manner similar to the human. Pharmacodynamic similarities are also important because the pathogenesis of atenolol embryo-fetal effects is associated with its pharmacodynamic action on utero–placental and fetal vasculature and hemodynamics.

Although the main pharmacokinetic/dynamic parameters are generally similar in humans and experimental animals, there are some differences that may affect the comparability of animal/human developmental toxicity (reviewed in Tabacova and Kimmel, 2002). Thus, transplacental passage of atenolol is lower in the rat than in the human, due to greater binding of the drug to rat plasma protein. There are differences between the hemodynamic effect of atenolol in hypertensive human subjects and rat hypertension models, as well as between the effect of the drug on glucose metabolism in rats and in humans. These differences may influence manifestations of developmental toxicity, considering the importance of glucose homeostasis during gestation and the recognized adverse effect of maternal hypertension on intrauterine development.

Higher vulnerability of the human conceptus is possible due to the greater passage of the drug across the human placenta because of the low binding of atenolol to plasma proteins in the human. Maternal hypertension, the main indication for atenolol use in pregnancy, could also be a reason for a higher vulnerability of the human fetus. Maternal hypertension by itself can induce changes in utero–placental and fetal hemodynamics, and hypertensive pregnancies are marked by high frequency of prematurity and growth restriction (Sibai et al., 1998; Kramer et al., 1999). Such effects are not likely to take place in standard experimental testing for developmental toxicity because, typically, normotensive animals are used.

Developmental toxicity manifestations. A comparison of outcomes of prenatal atenolol exposure in experimental animals and humans is presented in Table 6. Outcomes are grouped into categories of maternal toxicity, prenatal manifestations, and postnatal effects in experimental animals and humans. Both presence and absence of effects concordant in the tested animal species and in human subjects have been considered. Comparisons allowed us to make the following inferences.

Maternal exposure to atenolol has adverse effects on prenatal growth in human subjects and in mammalian animal species used routinely as experimental models in developmental toxicology (rat and rabbit).

Developmental toxicity in humans is observed at oral doses of atenolol lower (per kg of body weight) than those affecting the most sensitive endpoints of developmental toxicity in rats and rabbits by the same route of exposure.

Animal-to-human comparisons of maternal toxicity are hindered by pronounced animal–human disparities in the doses applied, and in the maternal endpoints observed. Atenolol is not maternally toxic in humans at doses in the therapeutic dose range (0.7–3 mg/kg/day). No maternal toxicity is seen in the rat at doses two orders of magnitude higher than the upper limit of the human therapeutic dose.

Table 6
Atenolol Developmental Toxicity: Animal to Human Comparisons

	Animal studies							
							Effect observed at exposures during:	
Endpoints	Adverse outcomes	Observed effect	Studies reporting effect/total (n)[a]	Species	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	Organogenesis only	Beyond organogenesis
Prenatal effects	Increased embryo/fetal loss	(±)	1/3	Rat	50	25	(+)	(−)
		(+)	1/1	Rabbit	25	10	(+)	ND
	Stillbirth	(−)	0/4	Rat	—	200	(−)	(−)
	Decreased fetal/birth weight	(±)	1/4	Rat	100	40	(−)	(+)
		(+)	1/2	Rabbit	1 (i.p)	25 (oral)	(−)	(+)
	Signs of intrauterine growth retardation	(+)	2/3	Rat	20	10	(±)	(+)[c]
	Altered placental weight	(+)	1/1	Rat	25	—	(+)	ND
		(+)	1/1	Rabbit	1 (i.p)	—	(−)	(+)
	Congenital malformations	(−)	0/3	Rat	—	200	(−)	(−)
		(−)	0/2	Rabbit	—	25	(−)	(−)
	Oligohydramnios	(−)	0/1	Rat	—	200	(−)	ND
Postnatal effects	Bradycardia	(+)	1/1	Rat	7.5	—	ND	(+)
	Decreased weight gain	(±)	1/3	Rat	100	40	(−)	(+)
	Retarded growth and development	(−)	0/2	Rat	—	20	(−)	(−)
	Neurobehavioral deviations	(±)	1/2	Rat	7.5	—	(−)	(+)
	Postnatal mortality	(±)	1/3	Rat	200	50	(+)	(−)

The pregnant rabbit seems to be more sensitive than the rat, however, because signs of maternal toxicity are present at much lower doses in the rabbit (on a milligram per kilogram basis).

Atenolol is a selective embryo-fetal toxicant in the human and the rat because in these species, developmental effects are induced by dose levels far below those causing maternal toxicity. In contrast, atenolol may have no selective embryo-fetal effect in the rabbit because adverse prenatal outcomes are induced only by doses that are maternally toxic.

The prenatal manifestations of atenolol embryotoxicity are similar in experimental animals and humans. Examples are decreased fetal weight, intrauterine growth retardation (manifested as retarded skeletal ossification in the rat), and, most notably, altered placental weight. Placental hypoplasia is thought to be a consequence of the pharmacodynamic effect of the drug on the utero–placental circulation. Animal–human concordance is also seen in the lack of effects on the incidence of congenital malformations in both animal species tested and in humans, as well as the absence of oligohydramnios (produced by other antihypertensive drugs, such as ACE inhibitors (Tabacova and Kimmel, 2002).

Although available data on postnatal manifestations of gestational exposures to atenolol are limited to one animal genus (rodents), they are suggestive of animal–human concordance. In the human, the most frequent complication in the early postnatal period is reduced heart rate (bradycardia) thought to be associated with atenolol pharmacodynamics. Although this endpoint is not tested routinely in animal postnatal assessments, the only study that measured neonatal heart rate in the rat found a statistically significant bradycardia in progeny of atenolol-treated dams during the first 24 hr after birth. In the rat, as in the human, no significant deviations in postnatal physical development were seen, but some neurobehavioral and developmental deficits were manifested in this species at maturity or upon environmental challenge. Such information is not available in humans; none of the studies has followed children of atenolol-treated mothers long enough to assess their development beyond early childhood. Such outcomes are not unlikely in the human, considering that intrauterine growth retardation (an outcome frequently associated with atenolol exposure) has been associated in humans with brainstem conduction time abnormalities (Sarda et al., 1992) and with developmental and academic problems persisting into adulthood, such as higher incidence of neurosensory deficits, poorer educational achievements, and a greater burden of illness (Hack et al., 2002).

Human studies					
				Effect observed at exposures during:	
Adverse outcomes	Observed effect	Studies reporting effect/total (n)[a]	Dose (mg/kg/day)[b]	First trimester only	Continued beyond 1st trimester
Spontaneous abortion	(−)	0/6	0.7–3	(−)	(−)
Stillbirth	(±)	2/11	0.7–3	(−)	(+)
Decreased birth weight	(+)	8/11	0.7–3	(±)	(+)
Intrauterine growth retardation	(+)	6/11	0.7–3	(−)	(+)
Decreased placental weight	(+)	5/5	0.7–3	(−)	(+)
Congenital malformations	(−)	0/12	0.7–3	(±)	(−)
Oligohydramnios	(−)	0/12	0.7–3	(−)	(−)
Bradycardia	(+)	3/6	0.7–3	(−)	(+)
Decreased weight gain	(−)	0/2	0.7–3	(−)	(−)
Retarded growth and development	(−)	0/2	0.7–3	(−)	(−)
Neurobehavioral deviations	(−)	0/1	1.5	ND	(−)
Postnatal mortality	(−)	0/10	0.7–3	(−)	(−)

LOAEL, lowest adverse effect level; NOAEL, no adverse effect level; (+), presence of effect; (−), absence of effect; (±), effect uncertain or statistically non-significant; (?), evidence insufficient to draw conclusions; ND, no data; —, LOAEL or NOAEL outside the tested dose range; i.p., intraperitoneal.

[a]Total n studies that measured the respective outcome.

[b]Calculated on the basis of human therapeutic dose range (50–200 mg/day for a person of 70 kg average body weight).

[c]Retarded skeletal ossification; renal pelvic enlargement.

The available data suggest a better concordance between the human and the rat than between the human and the rabbit with respect to manifestations of atenolol developmental toxicity. The human seems to be more sensitive because the administered maternal dose associated with adverse embryo-fetal developmental effects is lower in comparison to the rat; however, pharmacokinetic differences in bioavailability may account for the apparent greater sensitivity in humans. Less concordance is seen between the human and rabbit; in this species, atenolol exerts adverse embryo-fetal effects only at doses that are maternally toxic.

In conclusion, the animal studies were predictive of developmental toxicity manifested as placental changes, intrauterine growth retardation, and changes in fetal weight in the absence of structural malformations. Thus far, this is concordant with the data from humans in whom intrauterine growth retardation has been observed in the absence of structural abnormalities.

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