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Experimental investigation of possible cardiotoxic effects on the offspring of rats treated with high doses of fenoterol.

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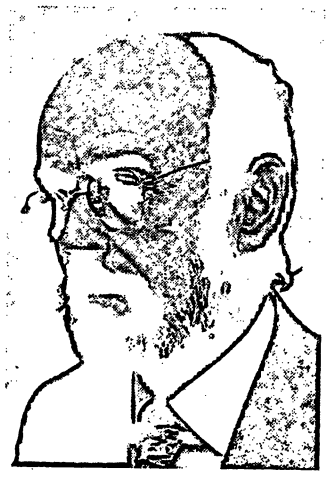
In animal experiments, high doses of catecholamines exhibit cardiotoxicity and can produce myocardial necroses (see review of literature by HECHT [4]) which are mediated by an excessive Ca^{++} influx into the myocardium. In contrast, the effect on the fetal heart following treatment of pregnant animals with catecholamines is largely unknown. In the investigations described here the following questions were to be answered:

1. Do high doses of the sympathomimetic fenoterol given to pregnant rats cause alterations in the weight and histological appearances of the hearts of fetuses and young animals similar to those described in adult animals by MARMO et al. [6]?
2. Does treatment with fenoterol and isoprenaline produce a rise in myocardial calcium influx in fetuses similar to that reported in mother animals by FLECKENSTEIN [2] and ARNDTS [1]?
3. What are the differences in concentration of fenoterol between fetal and maternal myocardium?

1 Materials and Methods

All investigations were carried out on rats of the Chbb: THOM (SPF) strain. Animals were maintained under standardised conditions (airconditioned, germfree rooms; environmental temperature 22°C ± 1°, relative humidity 55% ± 3; lightdark rythm 12 : 12 hours; Altromin – R® standardised dry feed pellets from Firma ALTROMIN GmbH, Lage/Lippe, and drinking water ad libitum).

Curriculum vitae



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For the anatomical and histological investigation, 20 pregnant rats were given fenoterol[1]) = 1 – (3,5-dihydroxy-phenyl)-2 ((1,4-hydroxy-benzyl)-ethyl)-amino)-ethanol-hydrobromide from the 18th to the 22st day of pregnancy (day of presence of sperms in vaginal smear = 1st day of pregnancy). A further 10 pregnant animals served as controls. Subcutaneous dosages were 5.5 and 11 mg/kg body weight/day. The substance was dissolved in 0.9% NaCl; the volume used was 0.5 ml/100 g body weight. Half of the animals were delivered by caesarean section, the other half delivered spontaneously and reared their young for three weeks.

[1]) PARTUSISTEN®, Manufacturer: C. H. BOEHRINGER SOHN, INGELHEIM.

After killing, the hearts of mothers, fetuses and young were removed and the ventricular weights determined. Absolute heart weights were analysed statistically using the t-Test, the relative weights by the U-test according to WILCOXON et al. [10].

The hearts were fixed in 5% neutral buffered formalin and embedded in Paraplast. Sections were stained with H. E., Masson's trichrome stain and Perl's method for iron. Frozen sections were stained with Fettrot 7B. All H. E. sections were examined additionally under polarised light according to the method of PILNY et al. [7]. The histological changes were graded arbitrarily according to the severity and extent of the lesions as follows:

1. Mild changes: recognised as focal areas of interstitial oedema with increased eosinophilia of individual myocytes, small collections of monocytes and histiocytes in the interstitium with slight haemosiderin deposition and slight collagen formation. These changes were confined to the subendocardial region of the left ventricle commencing at the apex.
2. Moderate changes: consisted of more marked degenerative changes in myocytes and more intense cellular infiltration with moderate haemosiderin deposition and collagen formation. These changes extended more deeply and more cephally in the wall of the left ventricle and interventricular septum, remaining focal in most instances.

Three groups each of five animals in the 21st day of pregnancy were used for the estimation of myocardial calcium influx. Group 1 (controls) received 0.2 ml physiological saline, group 2, 20 mg/kg body weight isoprenaline and group 3, 11 mg/kg body weight fenoterol subcutaneously. Simultaneously 10 μg/kg $^{45}CaCl_2$ (= 100 μCi/kg) dissolved in 0.5 ml saline was administered as a tracer. After 6 hours exposure, the rats were anaesthetized with ether and subjected to thoracotomy, as described previously by ARNDTS [1]. 5 ml blood were taken from the right atrium, heparinised and centrifuged. Then the heart was removed and the right ventricle was dissected and weighed. The fetuses were removed and decapitated. The blood of all individuals from each litter was pooled (0.5–1.0 ml), heparinised and centrifuged. The fetal hearts were dissected and weighed. The preparation of the tissue and plasma samples was published previously by ARNDTS [1]. The ^{45}Ca-content in the heart tissue was given as a percentage relative to the particular plasma activity (% A). Thus, for each animal, the absolute value of the ventricular sample was calculated as a percentage relative to the value of the plasma.

$$\frac{\text{cpm/g maternal heart}}{\text{cpm/g maternal plasma}} \times 100 = \% A_{\text{maternal}}$$

$$\frac{\text{cpm/g fetal heart}}{\text{cpm/fetal plasma}} \times 100 = \% A_{\text{fetal}}$$

The radioactivity in the fetal plasma was the average value of the pooled blood plasma from all animals in each litter.

Twenty pregnant animals were used for the estimation of fenoterol and its metabolites in the myocardium of dams and fetuses. The animals were divided into 4 groups each of 5 animals. Paired groups received daily 5.5 and 11 mg/kg fenoterol respectively subcutaneously from the 18th to the 22nd day of pregnancy. In one group of each pair only the last dose of fenoterol (22nd day) was radioactively labelled, the other group receiving five doses of radioactive substance (tritium labelling in position 1). We injected 0.1 ml/100 mg body weight. Solutions contained 5.5 or 11 mg ^{3}H-fenoterol/ml saline ($\triangleq$ 211.5 or 197.7 μCi/ml).

On the 22nd day of pregnancy the animals were anaesthetised with ether 1 hour after the last dose. After thoracotomy, the dams were bled by heart puncture and the hearts were then removed. The fresh weights of the hearts of all dams and fetuses were determined. The tissue levels of substance and metabolites combined were estimated from the radioactive content; the tissue level of the substance itself was determined by selective ion-pair extraction. The estimation of the radioactivity was carried out according to ROMINGER and POLLMANN [9]. The radioactivity levels determined were converted to quantities of substance using

the specific radioactivity of the applied solution and expressed as concentration levels with respect to the fresh weight.

2 Results

From the 30 pregnant animals, 367 offspring were obtained. 190 fetuses were obtained by caesarean section (69 from control dams and 121 from treated animals) while 173 live births and 4 stillbirths (66 live births from control dams and 107 live births and 4 stillborn from treated dams) followed normal delivery. Four young (1 from a control dam and 3 from treated dams) died during the three week post natal period. Canabalism was the immediate cause of death in most cases.

After subcutaneous administration of 5.5 and 11 mg/kg body weight fenoterol, slight but statistically significant increases in the mean heart weights of treated dams were found (Tab. I). No differences in heart weights were seen in the fetuses and young in comparison to the controls. The histopathological findings are summarised in Tab. II. All control females showed normal histological appearances. Of the 20 females given fenoterol subcutaneously, 10 showed moderate changes, the remainder exhibiting only mild alterations. Infarct-like areas of myocardial necrosis were not seen in any of the animals.

In contrast, all of the 359 fetuses and newborn examined (133 control: 226 treated), including 3 stillbirths and 1 neonatal death, showed normal histological appearances.

Tab. III summarizes the treatment and the ^{45}Ca-uptake in maternal and fetal hearts (% A) following s.c. injections of isoprenaline, fenoterol or saline to pregnant rats. A total of 204 fetal hearts were measured. No effect on ^{45}Ca-uptake in any fetal ventricle, independent of the drug administered, is seen.

The reliability of our technique is demonstrated in column (e) of Tab. III. We confirmed those effects of isoprenaline on the myocardial ^{45}Ca-uptake previously published by FLECKENSTEIN [3]. These results demonstrate a higher cardiotoxicity of isoprenaline than of fenoterol. Adult male rats are more sensitive than female, non pregnant females more than pregnant.

The fenoterol and metabolite concentrations determined in the maternal and fetal heart are summarised in Tab. IV. The concentrations of metabolites of fenoterol (two isomeric glucuronides,

Tab. I. Absolute and relative heart weights of dams, fetuses and young.

Dosage group	Mean body weight (g) of dams (n = 5)	Mean heart weight of dams absolute (mg)	relative (%)	Mean body weight (g) of fetuses/young	Mean heart weight of fetuses and young absolute (mg)	relative (%)
Caesarean section study:						
Control	$\bar{x}$ 383.40 SD 20.46	$\bar{x}$ 711.1 SD 79.1	0.322	5.21	25.6	0.491
5.5 mg/kg	$\bar{x}$ 388.80 SD 37.42	$\bar{x}$ 1027.5 SD 257.6	0.460*	5.25	30.3	0.577
11 mg/kg	$\bar{x}$ 390.20 SD 37.28	$\bar{x}$ 973.5** SD 108.1	0.421	4.92	28.3	0.576
3 week post natal study:						
Control	$\bar{x}$ 382.00 SD 18.29	$\bar{x}$ 768.5 SD 54.2	0.345	38.43	153	0.398
5.5 mg/kg	$\bar{x}$ 378.50 SD 44.48	$\bar{x}$ 870.8* SD 52.3	0.380	44.28	171	0.386
11 mg/kg	$\bar{x}$ 383.60 SD 22.51	$\bar{x}$ 879.5* SD 65.5	0.393	41.43	170	0.410

* = $p < 0.05$ ** = $p < 0.01$

Tab. II. Histological findings in hearts of dams, fetuses and young.

Dosage group	Nr. per group	dams histology grading			Nr. per group	fetuses and young histology grading		
		normal	+	++		normal	+	++
Caesarean section study:								
Control.	5	5	–	–	68	68	–	–
5.5 mg/kg	5	–	1	4	60	60	–	–
11 mg/kg	5	–	–	5	59	59	–	–
3 week post natal study:								
Control.	5	5	–	–	65	65	–	–
5.5 mg/kg	5	–	5	–	48	48	–	–
11 mg/kg	5	–	4	1	59	59	–	–
Total	30	10	10	10	359	359	–	–

Tab. III. Myocardial ^{45}Ca-uptake in maternal and fetal right ventricles following subcutaneous isoprenaline, fenoterol or saline (expressed as % A).

Dam [a]	treatment [b]	^{45}Ca-uptake in maternal ventricles [c]		^{45}Ca-uptake in fetal ventricles [d]			^{45}Ca-uptake in ventricles of adult rats [e]	
		% A	mean*	(N) fetuses per litter	mean % A	± S.D.	male mean* (N=5)	non pregnant females, mean* (N=5)
1	saline	31		13	41	± 4.7		
2	saline	39		16	39	± 6.9		
3	saline	35	35 ± 2.8	13	37	± 3.6	34 ± 6.1	32 ± 2.7
4	saline	35		15	44	± 5.6		
5	saline	35		16	43	± 5.3		
6	isoprenaline 30 mg/kg	95		12	42	± 3.9		
7	isoprenaline 30 mg/kg	63		16	45	± 4.9		
8	isoprenaline 30 mg/kg	73	75 ± 12	14	45	± 5.3	215 ± 53.2	120 ± 13.6
9	isoprenaline 30 mg/kg	70		16	43	± 3.5		
10	isoprenaline 30 mg/kg	72		7	44	± 6.1		
11	fenoterol 11 mg/kg	35		13	40	± 3.9		
12	fenoterol 11 mg/kg	50		15	40	± 3.0		
13	fenoterol 11 mg/kg	41	46 ± 11	11	43	± 4.8	108 ± 35.6	61 ± 8.7
14	fenoterol 11 mg/kg	63		15	40	± 6.2		
15	fenoterol 11 mg/kg	41		12	47	± 3.9		

* ± S.D. (standard deviation)

POOK et al. [8]) in fetal hearts lie at one tenth of the maternal values. In contrast, the fenoterol concentrations in the hearts of fetuses are 1/200th to 1/500th of the values found in maternal hearts. While the concentrations of fenoterol in maternal and fetal hearts did not differ after single or multiple ^{3}H-fenoterol administration, the concentrations of fenoterol metabolites after multiple administration were clearly raised.

3 Discussion

The questions we raised regarding the effects on the hearts of the fetuses and young of pregnant

Tab. IV. Concentration of fenoterol and fenoterol metabolites in maternal and fetal heart tissue of rats*.

Dosage group	fenoterol conc. (ng/g)		metabolite conc. (μg/g)	
	dams	fetuses	dams	fetuses
5.5 mg/kg: one dose tritiated	518 ± 83	1.0 ± 0.5	1.183 ± 0.123	0.090 ± 0.018
5.5 mg/kg: all doses tritiated	847 ± 420	5.1 ± 2.6	1.683 ± 0.399	0.151 ± 0.021
11 mg/kg: one dose tritiated	1069 ± 335	2.2 ± 0.8	2.270 ± 0.349	0.152 ± 0.035
11 mg/kg: all doses tritiated	1027 ± 393	1.8 ± 0.6	3.174 ± 0.611	0.387 ± 0.036

* Mean ± standard deviation, n = 5

rats given high doses of fenoterol can be answered as follows:

1. Fenoterol, given subcutaneously up to a maximum of 10.000 times the human therapeutic dose, has no effect on the absolute or relative ventricular weights of fetuses or young. A slight, but nonetheless statistically significant increase in heart weight was found in dams. The histological findings are largely in agreement with these results. No histological evidence of myocardial damage was found either in newborn or 3 week old animals.
   Although the high subcutaneous doses of fenoterol produced mild to moderate changes in maternal hearts, infarct-like areas of myocardial necrosis typical of catecholamine toxicity were not seen. Indeed MARMO et al. [6] were unable to produce such necrosis in adult rats given 100 mg/kg body weight of fenoterol, intramuscularly, daily for 4 days. The cardiotoxic effect of sympathomimetics is mediated by an excessive Ca^{++} influx into the myocardium, activating contractility and exhausing the ATP stores.
2. No increase in myocardial calcium influx was seen in fetuses from dams treated with fenoterol. Isoprenaline also did not cause a rise in fetal myocardial influx. Thus, the in vitro catecholamine sensitivity demonstrated by KAUFMANN et al. [5], using isolated embryonal chicken hearts, can not be shown to produce cardiotoxic effects on the fetal heart in vivo.
3. Marked differences have been shown between the tissue concentrations of fenoterol and its metabolites in maternal and fetal hearts. Very low concentrations were found in the fetuses. As shown by the estimation of the concentrations of fenoterol and its metabolites in dams and fetuses, the placental transfer of fenoterol to the fetus is markedly reduced. No accumulation of fenoterol in the fetal heart is demonstrated after daily subcutaneous injection of the mother for 5 days. The transfer of fenoterol metabolites is also markedly impaired, although not to the same extent as the substance itself. The mechanism responsible for the impairment of the placental transfer has not been determined.

The exceptionally low concentrations of fenoterol in the fetal hearts explain why the dosages used, although affecting the dams, were not cardiotoxic in the fetuses.

Summary

It was intended to determine, whether high doses of the sympathomimetic tokolytic drug fenoterol (PARTUSISTEN®) cause cardiotoxic effects in fetuses following administration to pregnant rats. We investigated in fetuses the following details:

1. Is there any myocardial necrosis or an increase of cardiac wheight?
2. Is the fetal myocardial ^{45}Ca-uptake increased to the same degree as in adult rats?
3. Is there any diaplacental transfer of fenoterol?

1. For morphological study, 20 pregnant rats were given either 5.5 or 11 mg/kg/day of fenoterol subcutaneously from the 18th to the 22nd day of pregnancy. From 10 rats the fetuses were taken by caesarean section and sacrificed immediately. The remaining rats were allowed to deliver normally and rear their young for 21 days. The absolute and relative heart weights of dams., fetuses and young were determined and statistically analysed. Routine and specially stained sections were examined by direct and polarised light microscopy.
2. The myocardial $^{45}Ca^{++}$-influx was determined at the 21st day of pregnancy. 5 pregnant rats received s.c. saline, 30 mg/kg isoprenaline or 11 mg/kg fenoterol. To all animals 10 μg/kg $^{45}CaCl_2$ (dissolved in 1 ml saline) was given i.p. After 6 hours radioactivity was determined in the right ventricle and in the blood plasma from dams and fetuses. The absolute radioactivity of the ventricle was calculated as a percentage relative to the plasma value.

3. Fenoterol and its metabolites were determined in the myocardium from 2 groups of rats and fetuses following s.c. injections of 5.5 or 11 mg/kg fenoterol from the 18th to the 22nd day of pregnancy. To 5 animals from each group radioactively labeled fenoterol was administered every day, the remaining 5 rats of either group received only one single radioactive injection at the 22nd day. One hour after the last injection the concentrations of both fenoterol and its metabolites were determined in the myocardial tissue.

1. The heart weights of fetuses and young from rats pretreated with fenoterol were exactly the same as from control animals (Tab. I) though the weights of maternal hearts were slightly but significantly increased. **None of the fetuses or young examined showed histological evidence of myocardial damage (Tab. II).** The treated dams showed mild to moderate myocardial changes. Infarct-like areas of myocardial necrosis were not observed in any of the animals.

2. **Neither fenoterol nor isoprenaline caused increased ^{45}Ca-uptake in the fetal ventricles.** The increase in myocardial calcium influx in fenoterol treated dams was considerably less than in those treated with isoprenaline (Tab. III). The tabulated results demonstrate further that adult male rats are more sensitive to catecholamine induced cardiotoxicity than females, non-pregnant animals more than pregnant.
3. **The diaplacental passage of fenoterol is strongly inhibited.** The concentration of metabolites in fetal hearts was approximately one tenth of that found in the dams; the analogue quotient for fenoterol itself is 1 : 100. There is no accumulation of fenoterol in the fetal myocardium even after multiple administration.

The absence of changes in the fetuses and young are to be explained by the very low placental transfer of fenoterol. It is quiet unknown by which mechanism the diaplacental transfer is inhibited.

Keywords: Calcium influx, diaplacental transfer, fenoterol, fetus, heart weight, myocardial necrosis, rat, tissue concentration.

Zusammenfassung

Experimentelle Untersuchungen zur Frage kardiotoxischer Effekte bei Nachkommen von Ratten, die mit hohen Dosen Fenoterol behandelt wurden.

Es sollte geklärt werden, ob hohe Dosen des sympathomimetischen Tokolytikums Fenoterol (PARTUSISTEN®) bei Feten subkutan behandelter Muttertiere kardiotoxisch wirkten. Folgende Detailfragen wurden untersucht: Kommt es nach hohen Dosen beim Feten zu

1. Zunahme des Herzgewichts oder zu Myokardnekrosen,
2. vermehrter myokardialer Radiokalziumaufnahme wie bei den Muttertieren
3. diaplazentarer Passage des Fenoterols?

1. Für die anatomischen und histologischen Untersuchungen wurde an 20 trächtige Ratten 5,5 bzw. 11 mg/kg Körpergewicht Fenoterol subkutan vom 18. bis 22. Trächtigkeitstag verabreicht. Von 10 Muttertieren wurden die Feten durch Kaiserschnitt entnommen und sofort getötet; die andere Hälfte warf ihre Jungen spontan und zog sie bis zum 21. Lebenstag auf. Es wurden die absoluten und relativen Herzgewichte von Muttertieren, Feten und Jungtieren bestimmt und statistisch geprüft. Die z. T. mit Spezialfärbung präparierten histologischen Schnitte wurden direkt und im polarisierten Licht mikroskopisch untersucht.
2. Der myokardiale Kalziuminflux wurde am 21. Trächtigkeitstag an 15 Tieren untersucht. Je 5 Muttertiere erhielten 0,85%ige NaCl-Lösung bzw. 30 mg/kg Isoprenalin oder 11 mg/kg Fenoterol subkutan. Als Tracer injizierten wir i.p. allen Ratten 10 µg/kg $^{45}CaCl_2$ (gelöst in 1 ml 0,85% NaCl). Nach 6 Stunden wurde die Radioaktivität im rechten Ventrikel und im Blutplasma von Feten und Muttertieren bestimmt. Die Radioaktivitätskonzentration im Ventrikel wurde auf diejenige im Plasma bezogen und in Prozenten angegeben.
3. Fenoterol und seine Metaboliten wurden im Myokard von Muttertieren und Feten an 2 Gruppen zu je 10 Tieren bestimmt, die vom 18.–22. Trächtigkeitstag 5,5 bzw. 11 mg/kg Fenoterol subkutan injiziert bekamen. Jeweils 5 Tiere aus jeder Gruppe erhielten an allen Applikationstagen radioaktiv-markiertes Fenoterol appliziert, die restlichen 5 Tiere je Gruppe nur eine radioaktiv markierte Dosis am 22. Tag. Eine Stunde nach der letzten Substanzgabe wurden die Gewebespiegel von Fenoterol und Metaboliten im maternalen und fetalen Myokard bestimmt.

1. Die fetalen Herzgewichte Fenoterol-behandelter Muttertiere unterschieden sich nicht von den Kontrollen (Tab. I). Geringgradige, jedoch statistisch signifikante Zunahmen der Herzgewichte wurde bei den behandelten Muttertieren festgestellt. **Weder Feten noch Jungtiere wiesen histologisch Myokardschäden auf (Tab. II).** Die Fenoterol-behandelten Muttertiere zeigten geringe bis mittelgradige Myokardveränderungen; infarktähnliche Bezirke wurden nicht festgestellt.
2. **Weder Fenoterol noch Isoprenalin verursachten eine Zunahme der ^{45}Kalziumaufnahme in fetalen Ventrikeln.** Die Zunahme des myokardialen Kalziuminflux Fenoterol-behandelter Muttertiere war beträchtlich geringer als die nach Isoprenalinbehandlung (Tab. III). Die tabellarisch erfaßten Werte zeigen weiter an, daß erwachsene männliche Ratten empfindlicher kardiotoxisch nach Katecholaminbehandlung reagieren als weibliche; nichtträchtige wiederum stärker als trächtige.
3. **Die diaplazentare Passage von Fenoterol und seinen Metaboliten ist stark gehemmt.** Während die Metabolitkonzentration im fetalen Myokard um eine Zehnerpotenz niedriger ist als im maternalen Myokard, beträgt der Konzentrationsunterschied beim Wirkstoff Fenoterol vom maternalen zum fetalen Myokard mehr als 2 Zehnerpotenzen. Eine Kumulation von Fenoterol im fetalen Myokard nach mehrfacher Applikation konnte nicht beobachtet werden.

Die fehlenden Veränderungen des Myokardgewebes bei Feten und Jungtieren können mit der äußerst geringen diaplazentaren Passage des Wirkstoffs Fenoterol erklärt werden. Welche Mechanismen diese Hemmung der diaplazentaren Passage bewirken, ist nicht geklärt.

Schlüsselwörter: Fenoterol, Feten, Gewebekonzentration, Herzgewicht, Kalziuminflux, Myokardnekrose, Plazentapassage, Ratten.

Résumé

Examens expérimentaux quant à l'éventualité d'effets cardiotoxiques chez la descendance de rates traitées à hautes doses avec du Fenoterol.

Il s'agissait de savoir si le sympathicomimétique-tocolytique Fenoterol (PARTUSISTEN®) appliqué à hautes doses par voie sous-cutanée chez des rates gravides a une action cardiotoxique sur les foetus. Les questions suivantes furent examinées: Aprés de hautes doses, observe-t-on chez les foetus

1. augmentation du poids du coeur ou nécroses du myocarde,
2. absorption augmentée du radiocalcium dans le myocarde, comme chez les méres
3. passage diaplacentaire du Fenoterol?

1. En vue des examens anatomiques et histologiques, 20 rates gravides reçurent des doses respectives de 5,5 et 11 mg/kg de poids corporel de Fenoterol par voie sous-cutanée, du 18ème au 22ème jour de gravidité. Une césarienne fut effectuée sur 10 animaux, les foetus recueillis furent immédiatement sacrifiés; l'autre moitié mit bas spontanément et éleva ses petits jusqu'au 21 ème jour de vie. Les poids absolus et relatifs des coeurs des mères, des foetus et des jeunes animaux furent déterminés et analysés sur le plan statistique. Les coupes histologiques préparées en partie avec une coloration spéciale furent examinées directement et à l'aide du microscope à lumière polarisée.
2. L'influx du calcium dans le myocarde fut examiné le 21ème jour de gravidité sur 15 animaux divisés en 3 groupes de 5. Chaque groupe reçut respectivement du sérum physiologique à 0,85%, 30 mg/kg d'Isoprenalin ou 11 mg/kg de Fenoterol en voie sous-cutanée. En tant que traceur, tous les animaux reçurent en i.p. 10 μg/kg de $^{45}CaCl_2$ (dilué dans 1 ml de NaCl à 0,85%). 6 heures après l'application, la radioactivité dans le ventricule droit et dans le plasma sanguin des foetus et des mères fut déterminée. La concentration de radioactivité dans le ventricule fut mise en rapport avec celle du plasma et exprimée en pourcentage.
3. La concentration de Fenoterol et de ses métabolites dans le myocarde fut déterminée chez les mères et les foetus de 2 groupes de 10 animaux ayant reçu par voie sous-cutanée des doses respectives de 5,5 et 11 mg/kg de Fenoterol, du 18ème au 22ème jour de gravidité. 5 animaux de chaque groupe reçurent du Fenoterol radioactif tous les jours d'application, les autres animaux n'eurent une application radioactive que le 22ème jour. Une heure après la dernière application, on détermina la concentration tissulaire du Fenoterol et de ses métabolites dans le myocarde maternel et foetal.

Résultats:

1. Les poids du coeur des foeteus avec mères traitées au Fenoterol ne se différencient pas du groupe de contrôle (Tab. I). On observa chez les mères traitées une augmentation faible du poids du coeur, néanmoins significative du point de vue statistique. **Ni les foetus, ni les jeunes animaux ne présentèrent des lçsions du myocarde á l'examen histologique (Tab. II).** On observa chez les mères traitées des modification faibles à moyennes du myocarde; des zones analogues à celles des infarctus ne purent être constatées.
2. **Ni le Fenoterol, ni l'Isoprenalin ne provoquèrent une augmentation de l'absorption du ^{45}Ca dans le ventricule foetal.** L'augmentation de l'influx du calcium dans le myocarde était nettement plus faible chez les mères traitées avec le Fenoterol que chez celles traitées avec l'Isoprenalin (Tab. III). Les valeurs exposées en tableaux montrent en plus que les rats mâles adultes réagissent sur le plan cardiotoxique plus sensiblement que les femelles après un traitement aux catécholamines; de même, les non-gravides réagissent plus fortement que les gravides.
3. **Le passage diaplacentaire du Fenoterol et de ses métabolites est fortement inhibé.** Tandis que la concentration des métabolites s'élève à une puissance dix fois plus faible dans le myocarde foetal que dans le myocarde maternel, la différence de concentration est supérieure à 2 puissances dix avec le Fenoterol lui-même. Une cumulation du Fenoterol dans le myocarde foetal après applications répétées ne put être observée. L'absence de modifications du tissu du myocarde chez les foetus et les jeunes animaux peut être attribuée au passage diaplacentaire extrêmement faible de la substance Fenoterol. On ignore quels mécanismes provoquent cette inhibition du passage diaplacentaire.

Mots-clés: concentration tissulaire, Fenoterol, foetus, influx du calcium, nécrose du myocarde, passage placentaire, poids du coeur, rats.

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