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Action of several β-adrenoceptor blocking drugs in the pregnant sheep and foetus

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Summary

1. The effect of several β-adrenoceptor blocking drugs on the pregnant ewe and foetus were studied. Bunolol, butidrine, oxprenolol, propranolol and USVP65-24 all crossed the ovine placenta and produced a β-adrenoceptor blockade in the ovine foetus. AH3474, AY21011 and sotalol did not cross the ovine placenta as assessed by the absence of a β-blockade in the foetus when these compounds were administered to the pregnant ewe.

2. Of the β-blocking compounds tested, only propranolol and oxprenolol produced a prolonged blockade in the foetus. The β-blockade with propranolol was of 3 h duration in the ewe and 10 h duration in the foetus. Oxprenolol produced a β-blockade of 3 h duration in the ewe and 8 h in the foetus.

3. The β-blocking drugs which did cross the ovine placenta were more soluble in organic solvents (ether, chloroform, corn oil and olive oil) than those which did not cross the ovine placenta.

Introduction

β-Adrenoceptor blocking drugs (β-blockers) have been used, together with catecholamines to aid in the control of uterine contractions during pregnancy (Eskes, Stolte, Seelen, Moed & Vogelsang, 1965 ; Stolte, Eskes, Seelen, Moed & Vogelsang, 1965 ; Barden & Stander, 1968). Coincident with their use in pregnancy, questions arise regarding the effects these β-blockers may have on the foetus. Obviously, the desired pharmacological effects of these compounds are on the uterus and any effects on the foetus are undesirable and if possible, should be avoided. Sethi & Chaudhury (1970) demonstrated that α-adrenoceptor and β-adrenoceptor blocking drugs did not alter fertility or implantation in rats. Untoward effects of these drugs on the foetus were not assessed in these investigations. However, depressed respiration has been reported in infants whose mothers received propranolol prior to delivery (Tunstall, 1969).

Preliminary investigations (Van Petten & Willes, 1968 ; Joelsson & Barton, 1969) demonstrated that propranolol crossed the ovine placenta and produced a β-adrenoceptor blockade (β-blockade) in the foetus. Further studies (Van Petten & Willes, 1970) showed that the duration of the β-blockade produced when propranolol was administered to the ewe was 2–3 times as long in the foetus as in the pregnant ewe. Due to the potential hazard of a persistent β-blockade in the foetus, especially at parturition, experiments were conducted to assess the action of several other β-blocking drugs in pregnant ewes and their foetuses.

Fitzgerald (1969) summarized the pharmacological properties of several β-blocking compounds and classified these drugs on the basis of their β-blocking activity, intrinsic sympathomimetic activity and quinidine-like or local anaesthetic activity. Using this classification and data of others (Marchetti, Merlo & Noseda, 1968; Blackburn, Byrne, Cullum, Farmer & Levy, 1969; Bauer & Michell, 1970; Levy & Wasserman, 1970; Robson & Kaplan, 1970), several β-blockers were selected for study and their effects on the pregnant ewe and foetus investigated to assess their ability to cross the ovine placenta and the duration of β-blockade they produce in the foetus as compared to the adult ewe.

Methods

Pregnant ewes of the Horn Dorset and Western Whiteface breeds of 110 to 120 days of gestation were surgically prepared with chronically implanted cannulae in the maternal and foetal carotid arteries and jugular veins and with sternal ECG electrodes on the foetus. The surgical procedures used were similar to those described previously (Willes, Manns & Boda, 1969; Willes, Van Petten & Truelove, 1970; Van Petten & Willes, 1970).

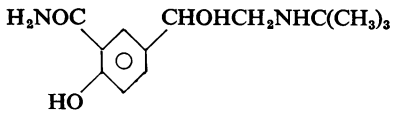
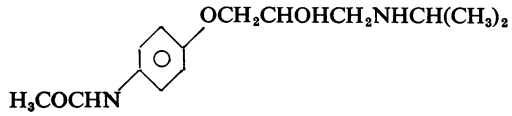
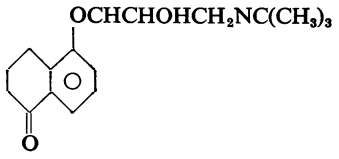
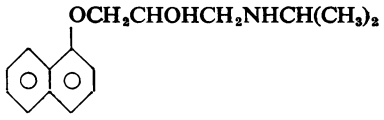
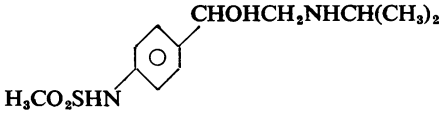
The dose of each β-blocking drug was chosen so that its duration of action would approximate the duration of β-blockade produced by 1 mg of propranolol/kg of body weight of adult ewe; that is a duration of 3 to 4 h (Van Petten & Willes, 1970). Each of the drugs was dissolved in 0·9% w/v NaCl, and infused into either the pregnant ewe or her foetus over a period of 20 minutes. The duration of β-blockade in the ewe and foetus was then measured by assessing the inhibition of the tachycardia produced when isoprenaline was administered intravenously to the ewe and to the foetus at several time periods (Van Petten & Willes, 1970). The dose of isoprenaline was 1 μg/kg except at 1 h after the β-blocker was given when 5 μg/kg of isoprenaline was given to the ewe and foetus to assess the efficacy of the β-blocker under investigation. All foetal doses of drugs were based on estimated foetal body weight (Stephenson, 1959).

At least 48 h elapsed between the surgical preparation of the ewe and foetus and the beginning of any experiments. In addition, at least 36 h elapsed between duplicate experiments on each animal to reduce any possible adverse effects of repeated doses of the drugs to the ewe and foetus.

To assess the relationship between the placental transfer of the β-blocking agents and their lipid solubility, the solubility of the β-blocking drugs in organic solvents was determined as described by Kato, Takanaka & Shoji (1969) with the following modifications. One mM solutions of the drugs in 0·05 M Na_2PO_4 (pH 7·4) were shaken with equal volumes (15 ml) of several organic solvents for 3 hours. The organic solvents included chloroform, petroleum ether, corn oil and olive oil. The concentration of the β-blocking drug remaining in an aliquot of the aqueous phase was measured by u.v. spectroscopy and expressed as a percentage of the concentration initially present in the aqueous phase.

The drugs used were AH3474 (Allen & Hanburys), AY21011 (Ayerst, McKenna & Harrison), bunolol (Warner-Lambert), butidrine (Simes), oxprenolol (Ciba), propranolol (Ayerst, McKenna & Harrison), sotalol (Mead-Johnson) and USVP 65-24 (USV Pharmaceutical Corp.). The formulae of these drugs are shown in Table 1.

TABLE 1. *β-Adrenoceptor blocking compounds chosen for study in the pregnant ewe*

β-Adrenoceptor blocking compounds	Chemical structure
AH3474	
AY21011	
BUNOLOL	
BUTIDRINE	
OXPRENOLOL	
PROPRANOLOL	
SOTALOL	
USVP65-24	

Results

The responses of the ewe and foetus to isoprenaline were similar to those reported previously (Van Petten & Willes, 1970). The intravenous administration of isoprenaline (1·0 μg/kg body weight) to the ewe and foetus produced maximum heart rates of approximately 290 beats/min and 310 beats/min respectively and concomitant decreases in blood pressure were observed in both the ewe and the foetus (Van Petten & Willes, 1970).

Generally, infusion of the β-blocker into the ewe resulted in a decreased heart rate in the ewe with little change in heart rate of the foetus (Table 2). The β-blockers infused into the foetus produced little change in heart rate in either the ewe or

TABLE 2. *Heart rates (HR; beats/min±S.E.M.) of dams (D) and foetuses (F) at various times after intravenous infusion of several β-adrenoceptor antagonists into the pregnant ewe. All β-adrenoceptor antagonists were infused over a 20 min period*

β-Adrenoceptor antagonist (Dose mg/kg)	Subject	Minutes after start of infusion of β-adrenoceptor antagonist										
		0	2	5	10	20	30	60	120	180	240	300
Propranolol (1·0)	D	102± 4	86± 3	81± 2	79± 2	79± 4	85± 3	85± 3	95± 4	98± 3	100± 5	104± 6
	F	182± 6	180± 8	167± 7	160± 3	150± 7	154± 8	155± 7	162± 8	169± 4	177± 5	187± 6
USVP65-24 (0·5)	D	105± 9	108± 6	96± 7	87± 3	87± 5	84± 3	84± 9	87± 6	91±10	91± 4	92± 7
	F	179± 7	183± 9	182±14	190±11	175± 4	170± 8	175± 4	175±12	173± 7	182±16	181±17
Bunolol (0·05)	D	118±10	121±10	114± 9	105±10	89±11	85±10	82±12	75±14	76±20	84± 8	82±17
	F	185±10	189±10	173± 7	186±12	177± 4	171± 7	171± 5	167± 5	164± 7	165± 7	168±13
Oxprenolol (2·0)	D	104± 8	101± 3	101± 2	94± 5	99± 4	—	91± 4	91± 2	105±10	102±13	108± 4
	F	168±11	164± 6	168± 3	169± 2	167± 3	—	166± 6	165± 6	161±11	151±15	166±10
Butidrine (2·0)	D	107± 3	105± 5	100± 1	101± 8	94± 8	93± 2	90± 3	97± 6	102±11	—	—
	F	162± 5	169± 4	155± 7	164± 7	158± 4	158± 3	160± 3	157± 6	153± 5	—	—
AY21011 (1·0)	D	124± 3	101± 9	100± 5	95± 7	98± 8	97± 6	98± 5	93± 4	92± 6	104±13	111± 4
	F	168± 9	165±12	171± 9	160±11	157± 9	163±13	160±10	167±13	163±12	160±17	160±20
AH3474 (5·0)	D	110± 5	107± 9	96± 6	93± 2	89± 2	97± 9	95± 2	102± 2	104± 2	107± 9	—
	F	162± 6	176± 2	174± 6	182±12	178± 2	165±10	172± 7	157± 3	179± 3	178±20	—
Sotalol (1·0)	D	97± 7	91± 7	85± 4	81± 2	79± 2	—	79± 2	79± 4	83± 2	83± 3	84± 4
	F	173± 8	182± 8	176± 5	174±12	167± 8	—	163± 5	163± 6	161±10	163± 7	160± 3

TABLE 3. *Heart rates (HR; beats/min±S.E.M.) of dams (D) and foetuses (F) at various times after intravenous infusion of several β-adrenoceptor antagonists into the foetus. All β-adrenoceptor antagonists were infused over a 20 min period*

β-Adrenoceptor antagonist (Dose mg/kg)	Subject	Minutes after initiation of infusion of the β-adrenoceptor antagonist										
		0	2	5	10	20	30	60	120	180	240	300
AY21011 (1·0)	D	112± 8	112±10	108±15	106±11	115±10	115± 8	120± 9	127±13	110±16	110±10	115± 6
	F	163± 3	164± 7	166± 4	169±14	172±14	176± 2	173± 3	170± 3	184± 8	168±10	157± 2
AH3474 (5·0)	D	103± 6	102± 5	100± 3	98± 8	105± 8	102± 2	107± 8	102± 2	97± 6	—	—
	F	169±11	171± 4	182±17	163± 8	159±12	162± 8	163±10	171± 5	159±10	—	—
Sotalol (1·0)	D	91±11	96±13	93±11	93± 8	98± 8	96± 6	103± 5	98± 5	93± 6	90± 2	92± 3
	F	155± 8	154±13	141± 7	137±10	142± 7	136±14	146± 8	148± 7	133± 7	138± 7	147± 5

foetus (Table 3). No significant effects of the β-blockers on blood pressure were observed in the ewe or the foetus.

The responses of the ewe and foetus to isoprenaline at various times after the i.v. infusion of the β-blockers are shown in Table 4. Propranolol resulted in a β-adrenoceptor blockade of 3 to 4 h duration in the ewe and 10 h duration in the foetus. The duration of β-adrenoceptor blockade following the i.v. infusion of USVP65-24, bunolol, oxprenolol and butidrine into the pregnant ewe were 5, 8, 3 and 3 h respectively in the ewe and 5, 8, 8 and 3 h respectively in the foetus (Table 4). These data demonstrate that USVP65-24, bunolol, oxprenolol and butidrine all crossed the ovine placenta and produced a β-adrenoceptor blockade in the foetus. With the exception of propranolol and oxprenolol, none of these β-blockers produced a prolonged β-blockade in the foetus as compared with the duration of blockade in the pregnant ewe. The duration of β-blockade produced in the foetus (8 h) by oxprenolol was approximately twice as long as that in the ewe (3 h).

The β-blockade produced by AY21011 (1 mg/kg) was of 8 h duration in the ewe but of less than 1 h duration in the foetus (Table 4). AH3474 and sotalol were effective in producing a β-blockade in the ewe but did not inhibit the effects of isoprenaline in the foetus. These results indicated that AH3474 and sotalol did not cross the ovine placenta while AY21011 crossed the ovine placenta only to a minor extent.

To substantiate that the lack of β-adrenoceptor blockade in the foetus following AH3474 and sotalol administration to the ewe was due to lack of placental transfer of these compounds, AH3474 and sotalol were administered directly to the foetus (Table 5). AY21011 was also given directly to the foetus to assess whether the short duration of β-blockade observed following maternal administration was due to a reduced rate of placental transfer of this compound (Table 5). Under these conditions, AY21011, AH3474 and sotalol produced a β-blockade in the foetus of 6, 4 and 8 hours duration respectively. No β-blockade was observed in the ewe when these compounds were given directly to the foetus.

One hour after the infusion of each of the β-blockers into the ewe, the efficacy of the blockade was assessed by challenging the ewe and foetus with a high dose of isoprenaline (5·0 μg/kg). In cases where the β-blocking compound did not readily cross the placenta (i.e. AY21011, AH3474 and sotalol) the foetus was not given the high dose of isoprenaline since high doses of isoprenaline, given in the absence of a β-blocking compound, were shown previously to cause ventricular fibrillation and death of the ovine foetus (Van Petten & Willes, 1970). The results (Table 6) showed that, at the doses used, all the β-blocking compounds tested inhibited the effects of isoprenaline to a similar extent. Likewise, at the dose tested, the duration of the β-blockade produced in the dam by the different compounds was similar. However, the doses of the β-blockers used were considerably different, therefore, the potency of the β-blockers in sheep from high to low potency would be as follows: bunolol, USVP65-24, (AY-21011, propranolol and sotalol), (oxprenolol and butidrine) and AH3474.

To assess the relationship between the lipid solubility of the β-blocking compounds and their ability to traverse the ovine placenta, the partition of the compounds between a buffered aqueous phase and several organic solvents were measured. There was a clear cut division of the compounds into two general groups

TABLE 4. *Maximum tachycardia (beats/min ± S.E.M.) of dams (D) and foetuses (F) produced by i.v. injection of isoprenaline (1 μg/kg) into the ewe and the foetus at various times after i.v. infusion of several β-adrenoceptor antagonists into the pregnant ewe. The control response to isoprenaline before giving the antagonist is shown at time 0. Each value represents the mean of at least 3 observations*

β-Adrenoceptor antagonist (Dose mg/kg)	Subject	Hours post-injection of β-adrenoceptor antagonist into the dam											
		0	0·5	1	2	3	4	5	6	7	8	9	10
Propranolol (1·0)	D	295± 6	—	170±10	202± 7	280±10	293± 7	295±10	—	—	—	—	—
	F	308± 9	—	200±10	200± 8	190± 8	180±13	190±10	220± 5	218±15	260± 8	298±7	306±8
USVP 65-24 (0·5)	D	267± 9	98·4± 3	186± 2	162±11	208±22	242± 6	260±11	280± 2	—	—	—	—
	F	305± 9	184±10	239±18	205±18	229±30	267±18	289±24	303± 8	—	—	—	—
Bunolol (0·05)	D	286± 6	—	160±22	119±12	129±10	147±18	161± 2	184±17	239± 2	290± 3	—	—
	F	291± 7	—	262±30	217±17	206± 4	241±18	239±20	254±28	264±32	291±12	—	—
Oxprenolol (2·0)	D	282± 7	—	163±21	224± 7	281± 9	283± 7	283±10	—	—	—	—	—
	F	309±13	—	201±18	197±19	244±17	219± 9	255±11	274±12	289±18	308± 9	—	—
Butidrine (2·0)	D	289±11	232± 9	260±11	273±11	290± 7	—	—	—	—	—	—	—
	F	306± 7	209±13	254±13	293±10	304± 3	—	—	—	—	—	—	—
AY21011 (1·0)	D	285± 8	143± 9	197±19	181±18	199±20	220±26	233±15	257±22	274±13	300± 9	—	—
	F	310±17	255±13	308±21	304±23	—	—	—	—	—	—	—	—
AH3474 (5·0)	D	291± 5	158±25	189±18	257±13	261±16	284±14	—	—	—	—	—	—
	F	281±17	282±13	275±13	286± 9	269±12	288± 9	—	—	—	—	—	—
Sotalol (1·0)	D	271± 8	—	123±13	146±22	174±15	191±20	202±10	225±17	251±12	283± 3	—	—
	F	277±12	—	280±17	272±20	277±11	273± 9	—	—	—	—	—	—

TABLE 5. *Maximum tachycardia (beats/min±S.E.M.) of dams (D) and foetuses (F) produced by i.v. injections of isoprenaline (1 μg/kg) into the pregnant ewe and the foetus at various times after the i.v. infusion of several β-adrenoceptor antagonists into the foetus. The control response to isoprenaline before giving the antagonist is shown at time 0. Each value represents the mean of at least 3 observations*

β-Adrenoceptor antagonist (Dose mg/kg)	Subject	Hours post-infusion of β-adrenoceptor antagonist into the foetus											
		0	0·5	1	2	3	4	5	6	7	8	9	10
Propranolol (1·0)	D	290± 6	292± 4	298±6	300± 7	—	—	—	—	—	—	—	—
	F	305±10	180± 7	200±8	237± 5	285± 5	285±10	300± 5	—	—	—	—	—
AY21011 (1·0)	D	287± 9	295± 5	287±3	—	—	—	—	—	—	—	—	—
	F	298± 5	199±25	197±4	222±20	224± 8	230±16	271± 3	291± 6	—	—	—	—
AH3474 (5·0)	D	295± 5	288± 3	293±2	—	—	—	—	—	—	—	—	—
	F	293± 3	192± 6	205±7	222±10	281± 6	298± 9	—	—	—	—	—	—
Sotalol (1·0)	D	293± 5	292± 2	287±5	287± 6	—	—	—	—	—	—	—	—
	F	302± 9	174±23	203±7	186±13	192±13	204±23	224±18	231±13	245±7	287±4	—	—

TABLE 6. *Maximum tachycardia (beats/min±S.E.M.) of dams and foetuses produced by i.v. injections of isoprenaline (5 μg/kg) into the ewe and/or the foetus one hour after i.v. infusion of the antagonist into the pregnant ewe or foetus. Each value represents the mean of 3 observations*

β-Adrenoceptor antagonist (Dose mg/kg)	Subject	β-Adrenoceptor antagonist infused into Dam	Foetus
Propranolol (1·0)	D	146±8	—
	F	140±5	—
USVP65-24 (2·0)	D	184±4	—
	F	213±8	—
Bunolol (0·05)	D	145±3	—
	F	178±4	—
Oxprenolol (2·0)	D	200±8	—
	F	201±2	—
Butidrine (2·0)	D	203±4	—
	F	202±8	—
AY21011 (1·0)	D	184±4	—
	F	—	213±7
AH3474 (5·0)	D	207±2	—
	F	—	214±6
Sotalol (1·0)	D	191±2	—
	F	—	205±8

TABLE 7. *Solubility of several β-adrenoceptor blocking drugs in chloroform, ether, olive oil and corn oil. Results expressed as percentage of the compound remaining in the aqueous phase after shaking for 3 hours*

β-Adrenoceptor blocking drug	% Remaining in aqueous phase Solvent Chloroform	Ether	Olive Oil	Corn Oil
Propranolol	6	25	7	31
Oxprenolol	11	73	49	78
USVP65-24	6·8	35	7·5	68
Bunolol	8·4	73	19	86
Butidrine	7	19	0	24
AY21011	98	96	100	100
AH3474	100	100	94	91
Sotalol	94	98	87	90

(Table 7). One group exhibited a high degree of lipid solubility and included propranolol, oxprenolol, bunolol, USVP65-24, and butidrine. These compounds showed a consistent high solubility in chloroform and ether. The solubility in corn oil and olive oil was more variable but still consistently higher than the second group of compounds. The second group of compounds exhibited a low degree of lipid solubility and included AY21011, AH3474 and sotalol.

Discussion

The prolonged β-blockade in the foetus when propranolol was administered to the pregnant ewe was consistent with previous observations (Van Petten & Willes, 1970). Of the other β-blockers tested, oxprenolol was the only one which showed a prolonged β-blockade in the foetus (8 h); this was approximately double that in the ewe (3 h).

Data on the efficacy of the β-blockade, obtained by administering isoprenaline (5 μg/kg) 1 h after i.v. infusion of the β-adrenoceptor blocking agent, demonstrated that propranolol and oxprenolol were no more potent as β-adrenoceptor blocking agents than were other compounds such as bunolol, AY21011, AH3474 or sotalol. These results show that the prolonged β-blockades observed in the foetus were due to characteristics of the compounds or their metabolites rather than a peculiarity in the β-receptor system of the ovine foetus. This conclusion is consistent with the observation that the isoprenaline dose-response curves are shifted equally to the right following a propranolol-induced blockade in the ewe and foetus (Van Petten & Willes, 1970).

A correlation was observed between the solubility in organic solvents, of the β-blocking agents tested and permeability of the placenta to the compound. Propranolol, USVP65-24, bunolol, oxprenolol and butidrine all showed a high solubility in chloroform, ether, corn oil and olive oil. All of these compounds crossed the ovine placenta as assessed by their ability to produce a β-adrenoceptor blockade in the foetus when administered to the pregnant ewe. AY21011, AH3474 and sotalol all showed a very low solubility in chloroform, ether, corn oil and olive oil and did not cross the ovine placenta as assessed by the lack of a β-blockade in the foetus when administered to the pregnant ewe. These observations are consistent with the generally accepted hypothesis that lipid solubility is one of the prime requisites regulating the transfer of a compound across biological membranes (Ginsburg, 1971).

The lower lipid solubility of AH3474, AY21011 and sotalol is also evident from their chemical structure. AY21011 and sotalol have hydrophilic groups in position 4 on the ring and AH3474 has such groups in positions 4 and 5. These side chains are not present on bunolol, butidrine, oxprenolol, propranolol or USVP65-24.

Oxprenolol and propranolol were the only two compounds tested which produced a prolonged blockade in the ovine foetus. These two compounds have identical side chains (Table 1). However, AY21011 and USVP65-24 also have the same side chain but did not produce a prolonged blockade in the foetus. Therefore, it is doubtful if the nature of the side chain was responsible for the prolonged blockade observed in the foetus.

Propranolol is known to be metabolized to 4 hydroxypropranolol (Fitzgerald, 1969 and Cooper & Hayes ; personal communication) and 4-hydroxypropranolol has been shown to possess β-blocking activity (Fitzgerald, 1969). The metabolic products of oxprenolol have not been investigated. The possibility cannot be discounted that metabolites of propranolol or oxprenolol may account for the prolonged β-adrenoceptor blockade in the ovine foetus when these drugs were administered to the pregnant ewe. Conceivably, the metabolic products could be formed within the foeto-placental unit although the levels of cytochrome P-450 (which is necessary for ring hydroxylation) are known to be very low in the liver of the ovine foetus (Clarke, Van Petten & Willes, unpublished observations). If these compounds were hydroxylated metabolites, if active they would have a low lipid solubility relative to the parent compounds and a prolonged β-adrenoceptor blockade could be expected in the ovine foetus due to an inability of the metabolites to be cleared from the foeto-placental unit. Further studies are necessary to investigate this hypothesis.

The data presented here demonstrate that it is unlikely that the prolonged β-blockade observed in the foetus is due to unique characteristics of the β-receptor system of the ovine foetus but is rather, due to characteristics of the compounds themselves.

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