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Effect of drugs used in obstetrics on the constriction by oxygen of the ductus arteriosus of the rabbit fetus*

E Endreffy, D Boda

Department of Paediatrics, University Medical School, Szeged, Hungary

The tone of the ductus arteriosus of the rabbit fetus near term constricted by oxygen (P_{O_2} = 20 kPa) was relaxed reversibly by the drugs chlorpromazine, promethazine, drotaverine, papaverine, diazepam, propanidid, isoxsuprine, pethidine, 5-ethyl-5-(1-methyl-propyl) 2-thiobarbituric acid, and furosemide. Ethyl alcohol, on the other hand, caused constriction of the fetal ductus arteriosus. These drugs if used in obstetrics may disturb the newborn's adaptation to extrauterine life by inhibiting the postnatal closure of the ductus arteriosus. On the other hand, the constrictive effect of alcohol may adversely affect the fetus. The results make it necessary to investigate the effect of the drugs applied during the perinatal period on the adaptation of newborns to extrauterine life.

The process of the constriction and closure of the ductus arteriosus (DA) shortly after birth has been given much attention in the literature. An important factor is the postnatal rise of oxygen tension in the newborn's blood [11, 16], but vasoactive materials (epinephrine, norepinephrine, histamine, bradykinin, serotonin, prostaglandins, etc.) released after birth also contribute to the effect [16].

The aim of the present examination was to investigate the influence of drugs used during delivery on the tone of the rabbit fetus DA constricted by oxygen in a perfusion system in vitro.

Materials and Methods

145 examinations were done on the DA of 56 fetuses delivered by Caesarean section from 37 hybrid pregnant rabbits at term. An in vitro perfusion system at 37 °C was used according to the method of Kovalčik [11]. The concentration of the constituents of the perfusion solution was NaCl, 118; KCl, 4.7; $CaCl_2$, 2.0; MgCl, 1.2; glucose, 4.5; and TRIS, 5.0 mmol/l. The pH of the solution was set to 7.4 by HCl. The perfusion solution was equilibrated with room air and N_2. Comparing the results obtained in a parallel examination with Tyrode solution, the response controlled with oxygen containing 5% CO_2 and with N_2 containing 5% CO_2 compared to the results found in TRIS buffered solution, no difference was observed in the response of the DA.

Perfusion at 16.9 $\pm$ 1.7 ml/min was kept up by a peristaltic pump (Peristaltic miniflow pump type 304 MTA Kutesz). The change in the perfusion pressure was measured by Statham transducer (Physiological pressure transducer P 2306) and recorded by Hellige electromanometer (Ma-88K) and MTA Kutesz 160-W. Functioning of the DA was tested by injecting 10 μg of norepinephrine into the system.

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In normal cases the drug elicited a contraction. Perfusion by a solution saturated with room air ($Po_2 = 20$ kPa) was followed by constriction, while saturation with N_2 caused relaxation and a repeated saturation with room air increased and settled the constriction.

The effect of the drugs on the DA was examined by measuring the change in perfusion pressure caused by the flow of the perfusion solution containing each drug in the appropriate concentration and saturated with room air. In dose-effect curve examinations the perfusion pressure before the test was taken as 100%, and the drug concentration bringing about a 50% change (mostly a decrease) of the perfusion pressure was determined by introducing perfusion solutions containing different concentrations of the drugs. Their mmol/l value was reckoned so as to reach ED_{50}.

As test substances the following drugs were used: buphenine HCl (Dilatol®, Troponwerke), isoxsuprine (Isoxsuprine®, Mead Johnson and Co), fenoterol (Partusisten®, Boehringer), diazepam (Seduxen®, Richter), propanidid (Sombrevin®, Richter), furosemide (Furantral®, Polfa), oxytocin (Oxytocin®, Richter), dihydralazine (Nepresol®, Ciba-Geigy), gallamine (Flaxedil®, Spécia), suxamethonium (Succinyl-Asta®), pethidine (Dolargan®, Chinoin),

TABLE I

Effect of drugs used in obstetrics on the constriction by oxygen of the ductus arteriosus (DA) of the rabbit fetus

Drug	No. of examination (complete dose-effect curve)	Smallest effective concentration (mol/l)*	ED_{50} mol** $\bar{X} \pm SD$	Observed effect on DA
1. Diazepam	10 (4)	7.0×10^{-7}	$6.0 \pm 7.0\times10^{-6}$	reversible relaxation
2. Pethidine	11 (2)	3.5×10^{-5}	1.8×10^{-4}	reversible relaxation
3. Papaverine	3 (1)	2×10^{-8}	5.2×10^{-8}	reversible relaxation
4. Drotaverine	9 (3)	4.6×10^{-7}	$2.2 \pm 1.5\times10^{-6}$	reversible relaxation
5. Chlorpromazine	6 (2)	1.0×10^{-7}	$6.2 \pm 4.0\times10^{-7}$	reversible relaxation
6. Promethazine	5 (1)	6.2×10^{-7}	1.4×10^{-6}	reversible relaxation
7. Propanidid	10 (2)	6.0×10^{-6}	$0.95 \pm 1.0\times10^{-4}$	reversible relaxation
8. 5-ethyl-5-(1-methyl-propyl)2--thiobarbituric acid	4 (1)	5.0×10^{-5}	4.0×10^{-4}	reversible relaxation
9. Lidocaine	9 (4)	2.5×10^{-4}	$5.0 \pm 2.7\times10^{-4}$	reversible relaxation
10. Furosemide	7 (2)	4.8×10^{-6}	$1.2 \pm 0.5\times10^{-5}$	reversible relaxation
11. Isoxsuprine	11 (5)	1.8×10^{-5}	$3.3 \pm 2.0\times10^{-5}$	reversible relaxation
12. Fenoterol	15 (—)	2.6×10^{-8}	—	partly irreversible relaxation
13. Ethyl alcohol	9 (—)	3.3×10^{-3}	—	hypertonicity
14. Buphenine	10 (—)	6.0×10^{-7}—1.0×10^{-5}	—	no effect in the concentration examined
15. Dihydralazine	4 (—)	3.5×10^{-6}—7.0×10^{-5}	—	no effect in the concentration examined
16. Oxytocin	10 (—)	0.2E—10E/l	—	no effect in the concentration examined
17. Gallamine	4 (—)	9.0×10^{-6}—9.0×10^{-5}	—	no effect in the concentration examined
18 Suxamethonium	8 (—)	2.2×10^{-6}—2.7×10^{-4}	—	no effect in the concentration examined

* In the case of the drugs Nos 14–18 the data show the concentration examined
** ED_{50}: drug concentration producing a 50% effect

lidocaine (Lidocain®, EGyT). The examined substances were chlorpromazine (EGyT), promethazine (EGyT), 5-ethyl-5-(1-methyl-propyl), 2-thiobarbituric acid (Chinoin), polioxethene ricinate (Richter), drotaverine (Chinoin), ethyl alcohol, noradrenaline (Richter), phentolamine, atropine sulphate and papaverine.

Results

Results are shown in Table I. Reversible relaxation of the DA followed the application of diazepam, pethidine, propanidid, 5-ethyl-5(1-methyl-propyl)2-thiobarbituric acid, furosemide, isoxsuprine, papaverine, chlorpromazine and promethazine. Buphenine, oxytocin, dihydralalzine, succinylcholine and gallamine did not cause any change in the tone of the DA.

Constriction of the DA occurred solely under the effect of ethyl alcohol. No dose-effect parallelism could however be found regarding the degree of constriction of the DA and the ethylalcohol concentration. Figure 1 illustrates the above described relaxing action by presenting a recording of the effect of furosemide which caused a dose-dependent, consistently reversible relaxation of the DA constricted by oxygen.

Discussion

The results showed that preparations widely used in obstetrics during delivery were, in most of the cases, affecting the DA of the rabbit fetus. It is an important question whether these drugs have a similar effect in the human newborn. To answer the question we must know whether these drugs passed through the placenta and, if so, would their concentration found to be active in vitro correspond to that in the newborn's blood.

Of the drugs studied, diazepam [11], 5-ethyl-5(1-methyl-propyl)2-thiobarbituric acid [14] and furosemide [2] are known to pass through the placenta and to result in a fetal blood level higher than the concentration that was found effective in the rabbit fetus. There are data available about the placental transfer of papaverine, drotaverine [12], chlorpromazine [8], promethazine [1] and propanidid [7] and about their blood level after a usual dose. In this case the blood level in the infants was higher than the concentration effective in vitro. Pethidine [6, 15] lidocaine [5, 14], isoxsuprine [4] and fentoterol [18] also penetrate across the placenta; their blood level after a usual dose was lower than their concentration which proved effective in vitro. Ethylalcohol was the only one among the drugs studied that caused a hypertonicity of the DA. Alcohol is known to pass across the placenta rapidly and even blood levels measured in a moderately alcoholic state were higher than the dose effective in vitro [3].

We have no data concerning the sensitivity in vivo of the DA to these drugs but as it is highly sensitive to prostaglandins and indomethacin [10, 17], it will probably react to other drugs in a similar way.

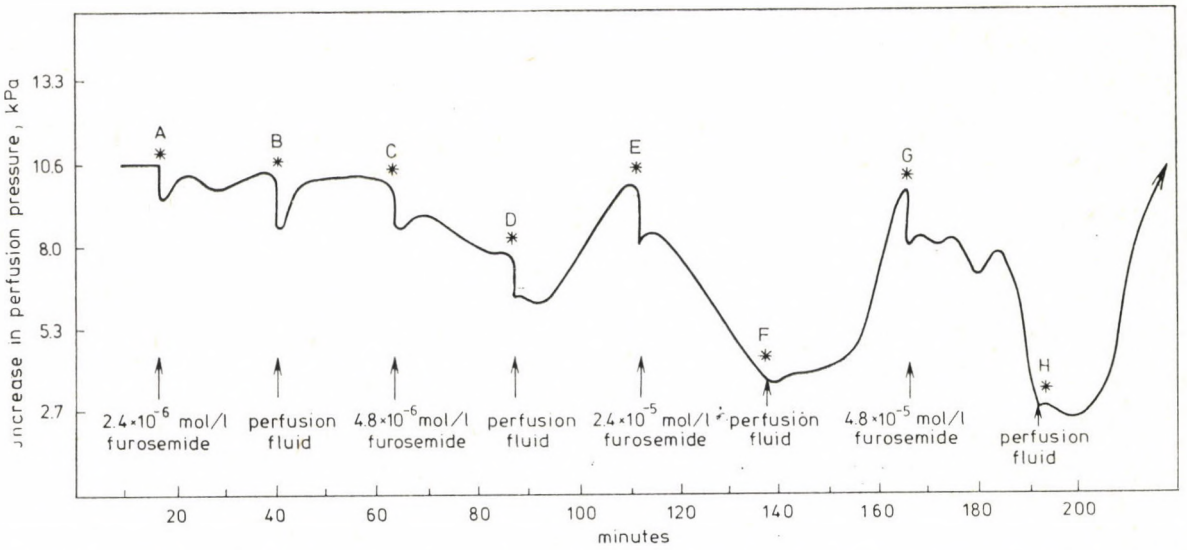

FIG. 1. The effect of furosemide on the DA of the rabbit fetus. Up to *A* perfusion solution saturated with room air (PO_2 = 20 kPa). $\overline{AB}$, $\overline{CD}$, $\overline{EF}$ and $\overline{GH}$ sections show DA relaxation on perfusion of solutions of increasing drug concentration. In $\overline{BC}$, $\overline{DE}$, $\overline{FG}$ and $\overline{H}$, administration of drug-free perfusion solution restores the original tone. The short decrease in pressure after change of the perfusion solution was due to technical factors

Most of the examined drugs were found to relax the DA. This effect may disturb the newborn's adaptation to extrauterine life and thus is represents a danger for the newborn, especially in pathological cases.

The hypertonic effect of ethylalcohol on the DA may affect the baby's further development. This possibility will have to be taken into consideration when prescribing infusions containing alcohol for delaying premature delivery.

These observations underline the necessity of further examinations to decide whether the drugs used in obstetrics would influence the closure of the DA of the newborn.

References

1. Adelman MH, Fisch H, Jacobson E, et al: Studies of promethazine with measurements of concentrations in venous blood fetal cord blood and cerebrospinal fluid. Anesthesiology 19: 93, 1958
2. Beermann BM, Groschinsky-Grind, Fahraeus L, et al: Placental transfer of furosemide. Clin Pharmacol Ther 24: 560, 1978
3. Belinkoff S, Hall OW; Intravenous alcohol during labor. Am J Obstet Gynecol 59:429, 1950
4. Brazy JE, Little V, Grimm J: Isoxsuprine in the perinatal period. II. Relationships between neonatal symptoms, drug exposure, and drug concentration at the time of birth. J Pediatr 98;146, 1981
5. Brown WU, Bell GC, Lurie AO, et al: Newborn blood levels of lidocaine and mepivacaine in the first postnatal day following maternal epidural anesthesia. Anesthesiology 42:698, 1975
6. Cooper LV, Stephen GW, Aggett PJA: Elimination of pethidine and bupivacaine in the newborn. Arch Dis Child 52:638, 1977
7. Doenicke A, Krumey I, Kugler J, Klempa J; Experimental studies of the breakdown of Epontol: determination of propanidid in human serum. Br J Anaesth 40:415, 1968
8. O'Donoghue SE: Distribution of pethidine and chlorpromazine in maternal, foetal and neonatal biological fluids. Nature 229:124, 1971
9. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE: Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med 295:526, 1976
10. Haram K, Bakke OM, Johannessen KH, Lund T; Transplacental passage of diazepam during labour: influence of uterine contractions. Clin Pharmacol Ther 24:590, 1978
11. Kovalčik V: The response of the isolated ductus arteriosus to oxygen and anoxia. J Physiol (Lond) 169:185, 1963
12. Magyar K, Lengyel M, Knoll J: Absorption, distribution and elimination of drotaverine. Acta Physiol Acad Sci Hung 51:401, 1978
13. McMurphy DM, Boreus LO: Studies on the pharmacology of the perfused human fetal ductus arteriosus. Am J Obstet Gynecol 109:937, 1971
14. Mirkin BL: Perinatal Pharmacology and Therapeutics. Academic Press, New York 1976
15. Morrison JC, Whybrew WD, Rosser SI, et al: Metabolites of meperidine in the fetal and maternal serum. Am J Obstet Gynecol 126:997, 1976
16. Moss AJ, Emmanouilides GC, Adams FH, et al: Response of the ductus arteriosus and pulmonary and systemic arterial pressure to changes in oxygen environment in newborn infants. Pediatrics 33:937, 1964
17. Olley PM, Coceani F, Bodach E: E-type prostaglandins: a new emergency therapy for certain cyanotic congenital heart malformations. Circulation 53: 728, 1976
18. Weidinger H: Labour Inhibition. G Fischer Verl, Stuttgart-New York, 1977, p. 47

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E Endreffy MD
P. O. Box 471
H-6701 Szeged, Hungary