Effect of Certain Drugs on Perfused Human Placenta I

Narcotic Analgesics, Serotonin, and Relaxin

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Perfusion studies conducted on full term human placentas yielded results indicating that morphine sulfate exhibited a direct vasoconstrictor action on placental vessels. This effect was also observed with meperidine hydrochloride and codeine sulfate, although the action of the latter agent was comparatively weak. Nalorphine hydrochloride antagonized the constrictor effect of morphine sulfate and codeine sulfate, but not that produced by meperidine hydrochloride. In addition, serotonin and relaxin both elicited powerful transient vasoconstriction.

IT IS GENERALLY concluded that the primary circulatory action of morphine is vasodilation, which is due to relaxation of blood vessels (1). Hypotension in cats and dogs (2), and cutaneous vasodilation of the flush area in man and animals (3) caused by morphine, support this concept. The mode of action for this effect is probably mediated centrally and peripherally and not directly upon the blood vessels involved, for vascular relaxation is not in accord with the principal action of morphine on smooth muscle elsewhere in the body which usually is stimulated to contract.

Many investigators, including von Euler (4), and Eliasson and Aström (5), have reported the effects of a number of drugs on perfused placental vessels, but there is no available information in the literature concerning the action of morphine on these vessels. Since morphine has been shown to have paradoxical actions on different smooth muscle, it becomes imperative to discern the effect that it may have on placental vasculature.

Narcotic analgesics, such as morphine (6), meperidine (7), and methadon (8), are well known to cross the placental barrier without much difficulty. Since this occurs with therapeutic dosage, the risk of neonatal respiratory depression is very high. With the advent of N-allylnormorphine (9), fortunately, respiratory depression, if present in the newborn, can be alleviated readily (6). Although the respiratory depression is undoubtedly due to the effect of the narcotic on the fetal respiratory center, the possibility arises that part of the depression may be due to decreased oxygenation of fetal blood brought about by a decreased blood flow through placental vessels which have been constricted by a direct acting drug.

The human placenta has been shown to be devoid of nervous tissue by Schmitt (10) and Spivack (11). Thus, it may be used as a nerve-free preparation in which direct effects of drugs acting on the smooth muscle of the linings of its blood vessels may be clearly elucidated. Therefore, it is the main purpose of this investigation to observe the effects brought about on the placental vasculature by not only morphine but also other narcotic agents, and in the event that there are direct effects, attempt to antagonize them.

MATERIALS AND METHODS

Full term placentas were obtained from the hospital within 5–15 minutes after normal delivery. Each was transported to the laboratory in a container of preheated (38°) Tyrode's solution which was modified by the addition of 0.525% polyvinylpyrrolidone (Plasdone C).

The preparation subsequently was flushed free of blood by injecting 10% sodium citrate solution into one of the arteries. Cannulae were inserted into the vein and one artery of the umbilical cord 5–10 cm. from the placenta. The remaining umbilical artery was ligated. The whole preparation was then placed into a perfusion chamber containing the modified Tyrode's solution which was maintained at a constant 37° by means of a Bronwill thermoregulator. The arterial cannula was connected with rubber tubing to a hydrostatic reservoir which was adjusted to yield pressures ranging between 50–60 mm. Hg. The solution in the reservoir, which had a pH range of 7.2–7.4, was maintained at 37° and aerated. The venous outflow, ranging between 10–60 ml./min., was measured directly and not reperfused.

A total of six placentas were discarded for quantitative reasons, i.e., the outflow per minute was either negligible or so far below the average preparation that it was considered impractical to measure.

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In 30 successful perfusion experiments the average duration of each preparation was between 2 and 3 hours.

The following drugs were injected into the rubber tubing adjacent to the arterial cannula in a volume of distilled water not exceeding 1 ml.: morphine sulfate, meperidine hydrochloride, codeine sulfate, nalorphine hydrochloride, 5-hydroxytryptamine creatinine sulfate (serotonin), relaxin, and alcoholic amyl nitrite.

RESULTS

Morphine.—Morphine sulfate in doses of 0.2–0.4 mg. (in eight preparations) had a pronounced constrictor action on the placental vessels. This effect (Fig. 1) was sustained and characterized by a slowly progressive decrease in the volume flow rate. The reduction in the flow rate ranged between 35–92% (Table I). Upon subsequent administration of 5 mg. of nalorphine, the morphine-induced vasoconstriction was antagonized, with the flow rate returning to near normal (Fig. 2, Table II).

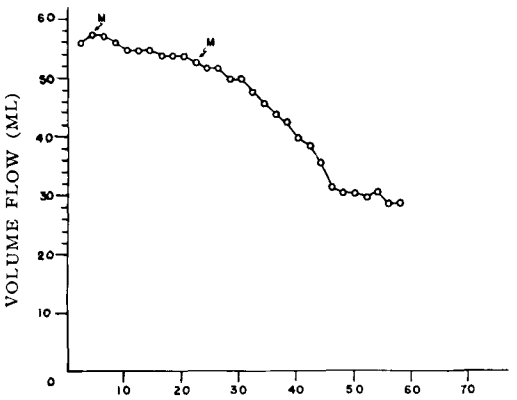

Fig. 1.—Effect of morphine sulfate on volume flow rate in vessels of the perfused human placenta. M, Morphine, 0.2 mg.

TABLE I.—COMPOSITE RESULTS

Drug	No. of Experiments	% Reduction in Flow Rate (Range)
Morphine	8	35–92
Meperidine	3	39–42
Codeine	3	6–11
Serotonin	5	19–61
Relaxin	3	59–84

TABLE II.—NALORPHINE ANTAGONISM OF NARCOTIC-INDUCED VASOCONSTRICTION

Drug	No. of Experiments	Av. % Return to Preinjection Flow Rate
Morphine-nalorphine	3	90
Codeine-nalorphine	3	91
Meperidine-nalorphine	2	0

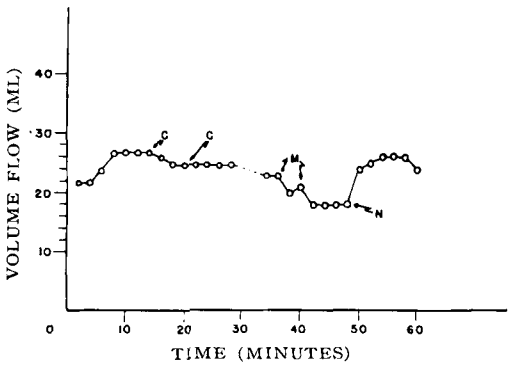

Fig. 2.—Effect of codeine sulfate and morphine sulfate on volume flow rate in vessels of the perfused human placenta and nalorphine antagonism. C, Codeine, 1.0 mg.; M, Morphine, 0.2 mg.; N, Nalorphine, 5.0 mg.

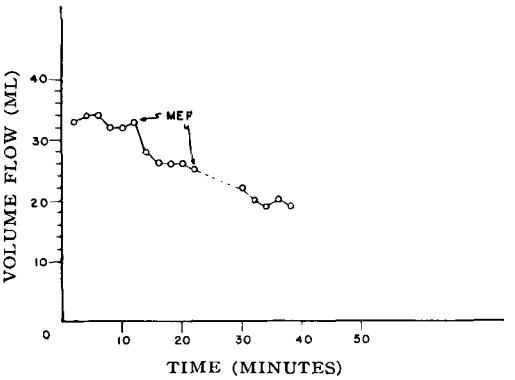

Fig. 3.—Effect of meperidine hydrochloride on volume flow rate in vessels of the perfused human placenta. MEP, Meperidine, 1.0 mg.

Meperidine.—In three experiments, meperidine hydrochloride in doses of 1–2 mg. produced a reduction in flow rate, as noted in Fig. 3, qualitatively similar to that which was observed with morphine. The per cent reduction in flow rate, which ranged between 39–42% (Table I), though not as great as that obtained with morphine, was also sustained.

Although meperidine produced a response akin to that of morphine, nalorphine was unable to antagonize it (Table II). However, the administration of 1 ml. of alcoholic amyl nitrite (1.8% v/v amyl nitrite) following nalorphine was successful in bringing about a marked increase in the flow rate.

Codeine.—Codeine sulfate in doses of 1–2 mg. (Fig. 2) produced a slight vasoconstriction in three preparations, resulting in a decrease in the flow rate of 6–11% (Table I). The administration of nalorphine antagonized this effect (Table II).

Nalorphine.—Nalorphine hydrochloride, 5–10 mg., used alone in a fresh preparation, was unable to exert any discernible effect on placental circulation. When it was administered prior to an injection of 0.2–0.4 mg. of morphine it was observed to block completely any vasoconstrictor action that this agent normally had on the placental vessels.

Serotonin.—In five experiments employing serotonin creatinine sulfate, a powerful vasoconstrictor of

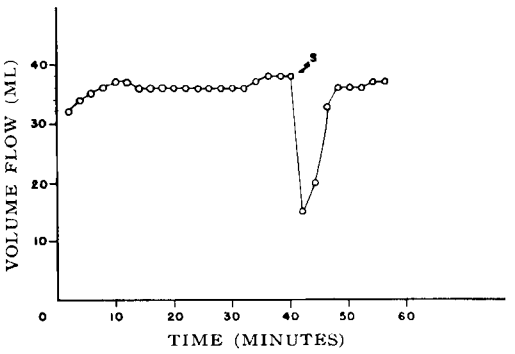

Fig. 4.—Effect of serotonin on volume flow rate in vessels of the perfused human placenta. S, Serotonin, 0.05 mg.

placental vessels, the results compared favorably to those of Astrom and Samelius (12) but the degree of constriction was not as marked. The dose of serotonin used was 50 mcg. in 0.5 ml. distilled water.

As seen in Fig. 4, after obtaining a consistent flow rate, the injection of serotonin caused an immediate decrease in this rate with almost a complete recovery to the preinjection level in approximately 6–8 minutes. The per cent reduction in the flow rate, as noted in Table I, ranged between 19–61 %.

Relaxin.—A dose of 1 ml. of relaxin[1] produced an immediate vasoconstriction in three preparations. The reduction in the flow rate produced by relaxin varied between 59–84% (Table I) during the succeeding 2 minutes. Most of this effect, although very pronounced, wore off in about 10 minutes.

DISCUSSION

The results of these experiments indicate that morphine exerts a direct constricting effect on the smooth muscle found in the linings of placental vessels. These findings are in contrast to the effects of morphine on other vascular beds where usually vasodilation is observed (2, 3). However, the constriction which occurred was analogous to that which morphine produces on gastrointestinal smooth muscle in that it was progressive and sustained.

Dornhorst, *et al.* (13), have shown that epinephrine and norepinephrine, in effective dosage, cause fetal asphyxia and cyanosis of the placenta in the rabbit and guinea pig. Because these conditions occur in response to drugs which act directly on placental vessels to constrict them, it may be concluded that any other agent which acts directly on these vessels causing vasoconstriction may also cause fetal asphyxia and placental cyanosis. Therefore, it is obvious that since morphine has been shown in this investigation to be capable of producing direct vasoconstriction in placental vessels, it may contribute partly to the fetal asphyxia sometimes caused by morphine. Of course the results reported here with morphine were those occurring *in vitro*, but it seems rather likely that similar effects would also be manifested *in vivo*.

Nalorphine was observed (Table II) to antagonize readily morphine-induced vasoconstriction in placental vessels, and it is probable that this would also occur *in vivo*. Consequently, its use *in vivo* would not only prevent central respiratory depression in the newborn but also any decreased oxygenation of fetal blood which may occur in response to the direct constricting action of morphine on these vessels.

The vasoconstrictor effect brought about by codeine in three preparations was very mild and susceptible to antagonism by nalorphine (Table II). Therefore, it would appear that fetal asphyxia due to codeine would be less marked than that produced by morphine and would be mainly due to just central respiratory depression.

Meperidine appeared to exert an effect on placental vessels that was similar to that produced by morphine. However, in the dosage employed, nalorphine was not able to antagonize the vasoconstriction caused by meperidine (Table II). Possibly if larger doses of meperidine were used, nalorphine may have exerted some antagonistic action, for it is well known that in order for nalorphine to cause withdrawal symptoms in the addict, at least 2,000 mg. must be ingested per day (14). Therefore, on this basis it seems likely that some antagonism of the constricting action of meperidine might have occurred if very large doses had been employed.

Serotonin was used in all preparations that were utilized as controls in this experiment. Five such preparations were set up and allowed to run for varying time intervals to discern any changes in the normal flow rate/min. through the placental vessels. In each case there was a period of 5–15 minutes where the flow rate increased slowly and then leveled off to a point where it would not change by more than 6% in one hour. In order to obtain effects similar to Astrom and Samelius (12), 50 mcg. of serotonin had to be administered. In each case a very profound vasoconstriction was observed which was greatest during the first 2 minutes immediately following the injection. This effect was transient, for within 4–5 minutes, the preinjection flow rate/min. was approximated. Succeeding doses of serotonin brought about a similar reduction in the flow rate as long as a sufficient time interval was allowed between injections. In a few instances, where serotonin administrations were made before the original flow rate was obtained, there occurred a diminished response to the usual vasoconstrictor effect which may be considered to be a tachyphylactic phenomenon.

Three placentas were treated with relaxin in order to observe whether this hormone of late pregnancy would cause any direct effect on placental vessels. In all cases a very pronounced constrictor action was observed. This action was transient, but the original volume flow rate/min. was never attained. This leads one to hypothesize that the constrictor effect of relaxin may be due to a contaminant in the tissue extract or even the relaxin itself. Should relaxin cause a constrictor effect *in vivo*, it may play an important role in fetal asphyxia.

The vasodilation which occurred with alcoholic amyl nitrite was probably due to the ethyl alcohol and amyl nitrite which are both known to exert a direct relaxing effect on smooth muscle. Nitrates (5) have been reported to cause a similar result on placental vessels, so these findings were anticipated.

[1] Marketed by Warner-Chilcott as Releasin.

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Comparison of the Gastrointestinal Absorption of Aluminum Acetylsalicylate and Acetylsalicylic Acid in Man

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The gastrointestinal absorption rate and biological availability of aluminum acetylsalicylate have been studied in human subjects by the urinary excretion method. Acetylsalicylic acid absorption from orally administered aluminum acetylsalicylate was found to be less rapid than from aspirin, probably due to the very slow dissolution of the aluminum salt in gastrointestinal fluids. In the form used in this study, aluminum acetylsalicylate was incompletely absorbed after oral administration. Dosage forms containing this drug must be carefully evaluated with respect to absorption rate and biological availability.

THE ALUMINUM salt of acetylsalicylic acid has been admitted recently to the National Formulary (1) and is used currently in a number of proprietary pharmaceuticals. According to the background information which accompanied the proposed monograph on aluminum acetylsalicylate (Al.ASA) at the time it was considered for admission to the National Formulary (2), the drug has several significant advantages over acetylsalicylic acid (ASA). These are greater palatability, stability, and absence of astringent taste or acetic odor which is often found with ASA. As a result of its relative inertness, Al. ASA is said to be compatible with many more drugs than is ASA.

Neither the official monograph, nor the introductory statement which accompanied it at the time of submission, made reference to any possible difference in the rate or extent of gastrointestinal absorption of Al.ASA as compared with ASA. Al.ASA is a constituent of certain proprietary pharmaceuticals which are intended, among others, for the relief of acute pain and fever. Since Al.ASA is practically insoluble in water (1, 3), the possibility suggests itself that the absorption rate of the drug from the gastrointestinal tract of man may be considerably less than the absorption rate of ASA. If this is the case, there is the further possibility that Al.ASA is absorbed only partially, and that a portion of the undissolved drug is excreted in the feces. Accordingly, the gastrointestinal absorption rate and biological availability of Al.ASA have been investigated and compared with those of ASA. The present communication reports the results of this investigation and also presents certain physical-chemical data pertinent to the interpretation of the biological observations.

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EXPERIMENTAL

Materials.—Acetylsalicylic acid U.S.P., aluminum acetylsalicylate N.F. With each drug, only the fraction passing through a 100-mesh sieve was used in the investigation. Both compounds were assayed colorimetrically (4) after alkaline hydrolysis and were found to contain 100 ± 0.5% of the theoretical amount of salicylate.

Absorption Tests.—Healthy male adults served as test subjects. Their weights and ages are listed in Tables I and II. In the initial absorption test utilizing nine subjects, the drugs were administered