INDUCTION OF LEGAL ABORTION BY INTRA-UTERINE INSTILLATION OF PARGYLINE HYDROCHLORIDE (EUTONYL)

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Summary. Injection of a single dose of 50 to 100 mg of the monoamine oxidase (MAO) inhibitor pargyline HCl (Eutonyl-Abbott) in 20 ml normal saline into the amniotic sac, produced spontaneous interruption of pregnancy on nineteen out of twenty patients during the 10th to 24th week of pregnancy.

The described method of therapeutic abortion could become the method of choice in advanced pregnancy, as the administration of MAO inhibitors is simple, the dosage relatively small and absolutely safe.

Local application of MAO inhibitors deprives the placenta and foetus of a specific protective mechanism and thus induces early and late abortion. It is the protective mechanism of MAO which normally prevents maternal catecholamines and serotonin from reaching the placental vessels (and the foetus) where they may contract the uterus, the placenta and their blood vessels.

INTRODUCTION

Indications for therapeutic abortions change with progress in medicine, but the method in most parts of the world is identical. The vaginal approach to therapeutic abortion is fraught with several hazards, including danger of perforating the uterus, haemorrhage, retention of placental fragments and infection. The likelihood of these complications increases sharply after the 12th week of pregnancy (Eastman & Hellman, 1961). In an attempt to minimize these hazards, different techniques of early delivery have been developed. The surgical approach accomplishes evacuation of the uterus by the vaginal route when the uterus is up to 12 weeks in size, and by the abdominal route when the uterus is larger.

In order to avoid surgical intervention in cases of more advanced pregnancy (3 to 4 months), intra-amniotic injections were proposed. In 1935, Boero advocated the injection of 40% formalin to interrupt pregnancy. In 1954, Stamm & De Watteville reported on the use of the 'Aburel Method' by withdrawing 100 ml amniotic fluid and replacing it with an equal quantity of hypertonic saline solution. In 1960, Svane claimed good results through instilling normal
saline into the uterus by way of the cervical canal. In 1962, Bengtsson & Csapo discussed the use of hypertonic saline solution in mid-pregnancy and the possible mechanism of its action, and in 1962, Wagner, Karker, Fuchs & Bengtsson reported a large series of cases of interruption of pregnancy by intra-amniotic instillation of hypertonic saline. Wood, Booth & Pinkerton (1962) used 50% glucose by intra-amniotic injection for interrupting pregnancy with no serious complications. There is no doubt that aspiration of amniotic fluid and injection of innocuous solutions are now being used fairly frequently and with apparently no serious harmful results (Greenhill, 1963–64), although the technical performance of these methods seems to be complicated and produces severe discomfort for the patient, since 100 to 200 ml liquid are usually injected.

A series of experiments in provoking abortion in pregnant animals has been

<table>
<thead>
<tr>
<th>No.</th>
<th>Patients' initials</th>
<th>Weeks of gestation</th>
<th>Indication for interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M.Y.</td>
<td>8</td>
<td>Rubella (induction unsuccessful)</td>
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<tr>
<td>2</td>
<td>A.M.</td>
<td>11</td>
<td>Rheumatic heart disease</td>
</tr>
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<td>B.Y.</td>
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<td>Chronic nephritis (renal failure)</td>
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<tr>
<td>4</td>
<td>G.D.</td>
<td>12</td>
<td>Mitral stenosis and insufficiency</td>
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<tr>
<td>5</td>
<td>H.R.</td>
<td>12</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>6</td>
<td>L.B.</td>
<td>12</td>
<td>Psychological disturbances</td>
</tr>
<tr>
<td>7</td>
<td>R.H.</td>
<td>12</td>
<td>Rubella</td>
</tr>
<tr>
<td>8</td>
<td>E.B.</td>
<td>15</td>
<td>Rubella</td>
</tr>
<tr>
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<td>G.F.</td>
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<td>Ablatio retinae</td>
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<td>B.B.</td>
<td>16</td>
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</tr>
<tr>
<td>11</td>
<td>R.L.</td>
<td>16</td>
<td>Acute psychosis</td>
</tr>
<tr>
<td>12</td>
<td>H.L.</td>
<td>17</td>
<td>Polycystic kidney</td>
</tr>
<tr>
<td>13</td>
<td>H.L.</td>
<td>18</td>
<td>Psychological disturbances</td>
</tr>
<tr>
<td>14</td>
<td>G.S.</td>
<td>20</td>
<td>Cardiac failure (congenital heart disease)</td>
</tr>
<tr>
<td>15</td>
<td>D.G.</td>
<td>20</td>
<td>Chronic glomerulo-nephritis (renal insufficiency)</td>
</tr>
<tr>
<td>16</td>
<td>L.D.</td>
<td>20</td>
<td>Essential hypertension+renal insufficiency</td>
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<tr>
<td>17</td>
<td>A.S.</td>
<td>22</td>
<td>Essential hypertension</td>
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<tr>
<td>18</td>
<td>I.L.</td>
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<td>Chronic glomerulo-nephritis</td>
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<td>19</td>
<td>B.S.</td>
<td>23</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>20</td>
<td>D.M.</td>
<td>26</td>
<td>Rheumatic heart disease</td>
</tr>
</tbody>
</table>

Table 1

INDUCTION OF LEGAL ABORTION WITH PARGYLINE

successfully performed by us. We found that intra-amniotically injected pargyline can produce foetal death in rats at any stage of gestation (Koren, Pfeifer & Sulman, 1965a) by a new mechanism (see 'Discussion' below). The above results encouraged us to investigate the action of this compound in pregnant women when therapeutic abortion was indicated. It is important to stress that pargyline is a safe drug which has been widely used in psychiatric practice and as a treatment for hypertension. It is administered per os in doses of 50 to 100 mg daily for long periods (Kline, 1963; Orvis, Tamagna, Horwitz & Thomas, 1963).

MATERIALS AND METHODS

Intra-uterine injections of pargyline-HCl were given to twenty women in whom pregnancy had to be interrupted for various reasons, as listed in Table 1. The quantity of pargyline-HCl varied. For pregnancies of 10 weeks or less,
50 mg in 20 ml sterile normal saline solution was used. This dose was increased by 15 mg for each subsequent week of pregnancy up to a maximum of 100 mg of pargyline in 20 ml sterile normal saline solution. The solution was injected rather quickly without previous aspiration. In most cases the patient did not feel the injection. In two cases, the patient had to receive an oxytocin drip on the 3rd day to accomplish expulsion. In three cases (20 to 22 weeks of pregnancy) injections were made through the abdominal wall after local anaesthesia. In all other cases the needle was introduced without previous dilation after routine cleaning of the vaginal wall and cervix with surgical tincture. The patients lay in the lithotomy position with the cervix exposed, the anterior lip of the cervix being grasped with a single-tooth tenaculum. In this way introduction of the needle could be performed without difficulty. An 18-gauge spinal needle and a 20 ml syringe were used. If there were no signs of abortion on the 4th day after the injection, the method was considered to have failed. All patients received 250 mg of tetracycline four times daily for 5 days together with the standard vitamin replacement therapy per os. In all cases surgical evacuation of the uterus following the abortion was performed. The patients were re-examined within a fortnight and were found to be in perfect condition. In all cases histo-pathological examination of the placenta was carried out.

RESULTS

Out of twenty patients, nineteen aborted after one intra-amniotic or intra-foetal injection, most of them within the first 3 days and three on the 4th day after the injection. The stages of pregnancy were as follows:

Seven women were pregnant for 12 weeks or less;
Thirteen women were pregnant for 13 to 24 weeks.

It is worth while stressing that all thirteen patients of the later stages of pregnancy aborted.
In one case of 8 weeks’ pregnancy the method failed and a dilation and curettage had to be performed. In the rest of the patients in this series, the cervix opened spontaneously to expel the foetus. In most cases the foetus and the placenta did not show any specific pathological changes. No serious complications were observed. Some patients complained of tension in the lower abdomen, and, at the time of abortion, of abdominal and back pains.

Out of four patients with temperature reaction, two had about 39° C on one occasion and the other two had a slight temperature reaction of about 36° C on 1 day only. No case of cervical rupture was observed. As a rule the bleeding in connection with the abortion was slight to moderate. As can be seen from Table 1, pargyline-HCl appears to be unsuitable for the induction of early abortions.

DISCUSSION

From our small group of twenty patients it appears that intra-uterine injection of pargyline is an effective method for interrupting pregnancy. In previous work on pregnant rats we found that a single dose of 2.8 to 4.6 mg/kg pargyline-HCl
injected into the amniotic sac kills the foetuses at every stage of pregnancy (Koren, Pfeifer & Sulman, 1965a). In our experiments on pregnant women we found that a single small dosage of 50 to 100 mg pargyline-HCl/patient produced interruption of pregnancy.

The mechanism of the pargyline reaction is based on the block it exerts on the endogenous monoamine oxidase (MAO) contained in the placenta and in the amniotic fluid where it has the function of protecting the foetus from the deleterious effect of maternal serotonin and catecholamines (Brzezinski, Koren, Pfeifer & Sulman, 1962; Koren, Eckstein, Brzezinski & Sulman, 1961; Koren et al., 1965b). A normally functioning placenta produces high quantities of MAO (Luschinsky & Singher, 1948), which protect the normal development of pregnancy from endogenous vasoconstrictor amines (Berger & Cavanagh, 1963). We have shown that this MAO is passed in large quantities into the amniotic fluid (Brzezinski et al., 1962).

Thus, the mechanism of interference of pargyline with pregnancy is not a direct one but it is mediated by abnormal accumulation of serotonin. We have similarly shown in women (Koren et al., 1965b) that the serotonin content of the placenta gradually increases during pregnancy. The enzymatic activity of placental monoamine oxidase (which destroys serotonin) shows a reverse tendency; it is high at the beginning of gestation and, gradually decreasing, it reaches the lowest level at term.

These observations would then suggest that serotonin plays a part no less important than that of oxytocin in the initiation of parturition. Such an action would be strictly local, as the oestrogenized uterus becomes hypersensitive to the contractile action of serotonin.

Waugh & Pearl (1960) injected serotonin into pregnant rats at the 14th to 17th day of gestation in a dose which killed about half of the mothers and produced 100% foetal mortality. The hypothesis that, in mice, the lethal and teratogenic effects of serotonin are secondary to its interference with placental function was suggested in 1964 by Honey, Poulson, Robson & Sullivan. The absence of serotonin in amniotic fluid in humans has been established by us (Koren et al., 1961), its continuous destruction being safeguarded by the presence of large quantities of monoamine oxidase in the placenta.

It is possible that serotonin affects pregnancy in two ways: (a) directly, by contracting the uterus and acting on the uterine contents (placenta, amniotic fluid, foetus); and (b) indirectly, by acting on the maternal brain, thus releasing oxytocic hormone from the hypothalamus. This assumption, however, requires further study. In any case, pargyline acts by abolishing the protective effect of the MAO present in the amniotic fluid and placenta. This results in abnormal accumulation of serotonin in the uterine cavity and induces abortion.

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REFERENCES