THE ROLE OF 'DUVADILAN' AS A UTERINE RELAXANT

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There are several clinical conditions in obstetrics and gynaecology which, in the absence of an anatomical abnormality or an obvious pathological entity, can be directly attributed to the untimely or abnormal contraction of the uterine musculature, failure of the cervix to relax or spasmodic contraction of the blood vessels. The treatment in such cases has to be, to a large extent, symptomatic and is concentrated towards obtaining relaxation of the excessive smooth muscle contractions.

Morphine has long been employed to depress myometrial activity (Greenhill, 1955). However, it is well known that morphine occasionally appears to clinically restore, rather promptly, the progress in a tardy labour. Besides this paradoxical activity of morphine, laboratory findings on the commonly employed dosage of morphine indicate that apart from the general sedative action it has very little, if any, predictable effect on the contractility pattern of the intact human uterus in late pregnancy and labour (Caldeyro-Barcia, et al 1955; and Eskes, 1965).

Transient relaxation of the hyperactive uterus has been obtained by the use of small doses of epinephrine (Rucker, 1925). However, the frequency of cardiovascular side-effects and the transient activity associated with the drug prevent its effective use in the management and control of premature labour. The same is true of certain other drugs, notably those in the phenethanolamine group which are known to be inhibitors of the smooth muscle but can not be used because of the associated sympathemimetic and cardio-vascular side-effects.

The use of progesterone in the treatment of threatened abortion was based on the observation that at or near term, the progesterone levels of the uterine blood and muscle show a steep fall and which may be the cause of uterine contractions, leading to initiation of labour. Progesterone applied to isolated strips of myometrium also leads to a quietening or paralysis of spontaneous or oxytocin induced contractions. However, Wagatsuma, *et al* (1967) in their in vitro studies on the pregnant rhesus monkey failed to demonstrate the efficacy of progesterone to control the uterine contractions even though the progesterone levels in both the myometrium

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as well as uterine venous blood, were 400-2,000 times higher than the normal amounts of hormone during pregnancy in these animals, and 20-100 times the normal amounts in human pregnancy. Such large amounts of the hormone show a definite paralysing effect within 5 to 30 minutes upon the contraction of isolated myometrial strips of pregnant human and rhesus monkey.

Isoxsuprine Hcl (Duvadilan) belongs to the Beta-phenyl-ethylamine group of epinephrine like compound, synthesised by Moed and Van Dijk (1956). The drug is known to have a selective action on the uterine musculature with minimal side-effects, and is also the only available drug which can be administered by intravenous infusion. The present study is an attempt to confirm the claims of the effectiveness of 'Duvadilan' in a variety of clinical conditions in obstetrics and gynaecology.

Material and Methods

The drug, Isoxsuprine Hcl, has been used in a variety of clinical conditions resulting from spasmodic contraction of the smooth muscle of the uterus and blood vessels in patients admitted to the Zenana Hospital, Jaipur. The dosage schedule and the route of administration employed in different clinical conditions have been variable, depending on the severity of the symptoms and the resultant complications. The observations have been recorded in patients presenting symptoms of (1) threatened abortion, (2) premature labour, (3) tetanic urterine contractions, (4) acceleration of labour, (5) rigid cervix, (6) toxaemia of pregnancy and (7) primary spasmodic dysmenorrhoea.

Observations

1. *Threatened abortion*

Isoxsuprine Hcl was used in 30 cases of threatened abortion in 8th to 20th week of pregnancy. The drug was given orally 60 to 80 mgm./day in divided doses, and the therapy was continued for at least 2 weeks after the uterine contractions had ceased. In 2 cases, the treatment was commenced by an intramuscular injection of 2 cc./10 mgm. of Isoxsuprine Hcl. In 8 cases, the therapy had to be repeated twice or thrice, by the oral route, dosage schedule being the same, at 24th to 28th week of pregnancy owing to the recurrence of the threatening (i.e. threatened abortion).

The drug was helpful in obtaining labour at term in 20 cases and at 34-36 weeks in 5 cases. The treatment however, had no effect in preventing the course of threatened abortion in 5 cases.

2. *Premature labour*

All the 35 patients in premature labour fulfilled certain criteria before Isoxsuprine therapy was started: (a) pregnancy, between 26 and 36 weeks, (b) dilatation of the cervix, less than 4 cm. along with bloody show and abnormal uterine contractions as evidences of premature labour, (c) membranes were intact. (d) absence of complications which would contraindicate the continuation of pregnancy.

The treatment was commenced by an initial dose of 60 to 80 mgm. of Isoxsuprine Hcl diluted in 500 cc. of

glucose-in-water, and given by intravenous infusion at the rate of 40 to 50 drops/minute. The uterine contractions ceased after a single infusion of 80 mgm. Isoxsuprine Hcl in 30 cases. In 5 cases, a second infusion of 80 mg./day had to be continued when labour was arrested. A watch was kept on the pulse rate and the blood pressure. The rate of infusion was reduced in one case, due to the presence of tachycardia accompanied by a fall in blood pressure. When labour was arrested, oral therapy of the drug, 60 to 80 mgm./day in three to four divided doses, was continued for at least 2 weeks, but in most cases for four to six weeks and in some cases until the end of the pregnancy. The results of the treatment are given in Table 1.

TABLE 1

Showing results of 'Duvadilan' therapy in premature labour

Results	Number of cases
Labour not arrested	5
Labour arrested 4 to 7 days	5
Labour arrested more than 7 days (premature infant)	10
Labour arrested (mature infant)	15
Total	35

Out of 35 patients, labour at term was attained in 15 and labour was postponed for 4 to 7 days in 5, and for more than 7 days in 10 patients. The treatment failed to check the course of premature labour in five cases, perhaps due to inadequate dosage and an early discontinuation of the infusion. Maternal hypotension was observed during the administration of the drug in one case. In this instance, the blood pressure promptly returned to normal following decrease in the rate of administration of Isoxsuprine. However, no ill-effects were noticed on the infant.

4. *Rigid cervix*

In the present study, 5 patients with 'rigid cervix' of a functional type were observed, in which an incomplete dilatation of the cervix was noticed during the progress of labour without any known cause. Two multiparae and three primiparae comprised the group, with a rigidity varying from moderate in 2 patients to severe in 3.

Isoxsuprine Hcl was given by an initial intramuscular injection in a dose of 5 to 10 mgm., supplemented by an oral therapy of 20 to 60 mgm. in 3 to 4 divided doses for 1 to 2 days. The response of the patients was good to excellent in 4. One multipara did not respond. The uterine contractions remained unaffected by small doses of the drug at term.

5. *Acceleration of labour*

Isoxsuprine Hcl was used in 10 primiparae at term to accelerate the progress of labour. The drug was administered at the onset of dilatation by intravenous infusion of 20 mgm. in 500 cc. of 5% glucose in water, at the rate of 50 to 60 drops/minute. The average duration of labour between the time of 2 to 4 cm. dilatation and the actual birth was 4 hours and 20 minutes, a reduction of about 50%. With strong and regular contractions in 2 women the duration of labour pains was considerably less and the birth weights varied from 3,000 to 5,002 gms.

6. *Toxaemia of pregnancy*

Fifteen patients with toxaemia of pregnancy were given 10 mgm./day of Isoxsuprine Hcl, by intramuscular route for 3 to 4 days, till the blood pressure came down to normal. Subsequently, a maintenance dose of 60 mgm./day was given orally, in divided doses, for 6 to 8 weeks. The medication had to be continued till the end of pregnancy in 8 patients. All patients showed beneficial effects of the drug with fall in blood pressure and increase in the urinary output with reduction of oedema. The administration of the drug was accompanied by supportive medication of diuretics, salt restriction and sedatives.

7. *Primary spasmodic dysmenorrhoea*

For the present study, 50 cases of primary spastic dysmenorrhoea were carefully selected. Each case was questioned in detail about the menstrual history, the time and severity of cramping in relation to the onset of menstrual flow and the consistency with which the cramping occurred. The psychological background of the patients was carefully assessed and a thorough examination was carried out to exclude any existing pelvic pathology.

The treatment was commenced with 40 mgm./day of Isoxsuprine Hcl, in four divided doses during the menstrual period. The dose was increased to 60-80 mgm./day during the subsequent periods, if the patients reported inadequate relief. Later, the patients were instructed to take the drug 24 to 72 hours before the expected onset of the menstruation. These patients received the drug for an average of approximately 3 consecutive periods. Because of the severity of menstrual cramping, 5 patients were given a single intramuscular injection of 10 mgm. at the time of initial examination to be followed up by oral therapy.

The average result reported by the patients was good. The drug had no effect on premenstrual tension or the emotional disturbances associated with dysmenorrhoea. Slight drowsiness was experienced by 7 patients and minimal epigastric distress by 10. There was no alteration in the duration of intensity of the menstrual bleeding.

Discussion

An ideal drug for the management of spasmodic conditions of the smooth muscle in obstetrics and gynaecology should possess the effectiveness of epinephrine, must have a more selective action on the uterine musculature and the effect should be more sustained while providing a wide margin of safety. In this context Isoxsuprine Hcl is the most effective drug available today having a two-fold action (Fig. 1). (1) Neurotropic effect, by stimulating Beta-adrenergic receptors, which are richly distributed in the uterine musculature and simultaneously inhibiting the Alpha-adrenergic receptors, (2) In large doses, the drug has a papaverine-like myotropic influence on the musculature of the uterus.

The strong myotropic, antispasmodic effect of 'Duvadilan' on the uterine myometrium of laboratory rats was first demonstrated by

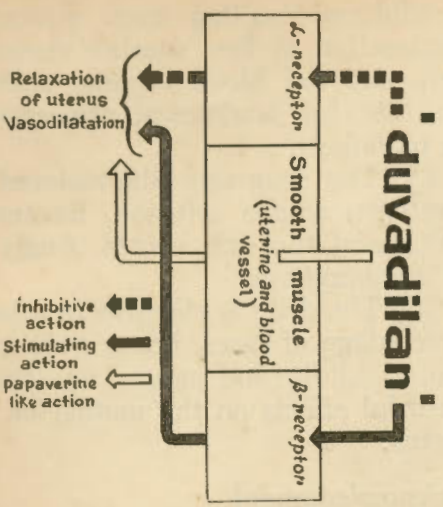

Fig. 1

Brucke, *et al* (1965). Lish *et al* (1960) later demonstrated that it effectively depresses the uterine activtiy of laboratory animals independent of the hormonal status of the uterus, including the pregnant uterus. They also demonstrated the effect of the drug (its sustained relaxant effect) on isolated strips of human uterus. Bishop and Woutersz (1961) and Alvarez Brave, *et al* (1962) observed the effects of the drug on human uterus during labour. They found the drug effective in the arrest of uterine contractions during premature labour in a large percentage of cases. The effect of Isoxsuprine Hcl is more pronounced and prolonged as compared to adrenaline (neurotropic effect) and papaverine (myotropic effect). With the advance of pregnancy, the uterine body and the cervix become more susceptible to the drug, but the two are not parallel. It has been established that the uterine body is more susceptible to the relaxant action of isoxsuprine than the cervix in an immature pregnancy but it is the cervix which can be readily relaxed by the action of the drug at full term pregnancy without affecting the uterine contractions unless the dose is too large (Suzuki, *et al* 1960). It is this property of the drug which also makes it useful in cases with tetanic uterine contractions and rigid cervix. The drug has also been successfully used to accelerate labour in suitable cases (Whitelaw, *et al*, 1961).

Isoxsuprine Hcl also affects the smooth muscle of the blood vessels, and is thus capable of improving placental circulation as well as the circulation of the uterine muscle by relaxation of the arterioles in spasm. This explains the usefulness of the drug in primary dysmenorrhoea and toxaemia of pregnancy (Suzuki, *et al.* 1960; Voulgaris, 1960; and Ratowsky and Padernacht, 1961). In pre-eclampsia, the hypertension is associated with or without renal damage and oedema as a result of vasoconstriction of renal arterioles. The pre-eclampsia may progress to eclampsia with vasoconstriction of cerebral vessels and the resultant convulsions. Similarly, the vasoconstriction of placental vessels may lead to foetal distress or even death. All these pathological processes in toxaemia of pregnancy can be counteracted by the administration of Isoxsuprine Hcl, unless the pathological processes have become irreversible. However, the drug only plays a supportive role and the importance of usual medication with salt restriction to counteract oedema and hypertension can not be overlooked.

Isoxsuprine Hcl therapy is not entirely without side effects. Stimula-

tion of Beta-adernergic receptors may cause an increase in the pulse rate, which within certain limits has a favourable effect by increasing the quantity of circulating blood. The inhibitory effects of the drug on Alpha-adrenergic receptors may cause a fall in blood pressure. The fall in blood pressure as observed in the present study was more marked when intravenous infusions were given and at a rate exceeding 0.5 mgm./minute. Well hydrated patients appear to tolerate infusion administration of the drug better than partially dehydrated ones. The maximum fall in blood pressure occurs within 6 minutes when the drug was given by the intravenous route and within 15 minutes when given by the intramuscular route. The fall in blood pressure and tachycardia can be counteracted by reduction in the rate of infusion and dose of the drug given. The oral therapy of 60 to 80 mgm./day of Isoxsuprine Hcl does not produce marked hypotension. The therapy is sometimes accompanied by mild dizziness, nausea and headache which are considered insignificant.

Whatever be the mode of administration, Isoxsuprine Hcl does not appear to produce any deleterious effects on the foetus. The drug thus holds out a promise of genuine usefulness in a variety of clinical conditions in obstetrics and gynaecology associated with spasmodic contractions of the smooth muscles of the uterus or the blood vessels.

Summary

(1) Isoxsuprine Hcl (Duvadilan) has been used in a variety of clinical conditions resulting from spasmodic contraction of the uterine musculature and the blood vessels, without any obvious anatomical abnormality or pathology.

(2) The drug was administered by the intravenous infusion, intramuscular and the oral routes, singly or in combinations.

(3) The drug is effective in a large percentage of cases, has a wide margin of safety and causes no serious harmful effects on the mother or the foetus.

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