She was hospitalized for fracture of the middle segment of the right femoral diaphysis, following a small trauma. Skeletal radiological studies showed a typical picture of polyostotic fibrous dysplasia, not only at the fracture site but in almost all the right hemisoma, whereas on the left there were only lesions in one rib.

DISCUSSION

We should like to emphasize the problems of the use of oral contraceptives in McCune-Albright syndrome. During pregnancy there is the risk of a worsening of bone lesions with pathologic fractures ([5, 6]), indicating the use of contraceptive methods, not in order to peremptorily exclude a pregnancy from which a baby not affected with this syndrome which is certainly not hereditary will be delivered ([7]), but in order that the patient may be fully aware of the risks a pregnancy could involve.

As stated by Kaplan F. S. *et al.* ([6]), the discovery of the presence of estrogen and progesterone receptors in the fibrous dysplasia lesions suggests a link between hormonal fluctuations and bone lesions in the McCune-Albright syndrome. For these reasons we judge the use of oral contraceptives to be "dangerous" (either of combination type or with progestogen only) in fertile women with this syndrome, in that an alteration of the physiologic hormonal pattern takes place: the fact that our patient was taking the "pill" at the time of the fracture may not be coincidental. The affected women must therefore be orientated towards alternative contraceptive methods.

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RANITIDINE IN THE TREATMENT OF REFLUX OESOPHAGITIS IN PREGNANCY

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Summary: A patient suffering from reflux oesophagitis under treatment with ranitidine continued the treatment throughout her pregnancy (450 mg/die). The ranitidine was delivered into the maternal blood serum and the amniotic fluid up to the 17th week of pregnancy, then into the blood serum of the maternal and umbilical cord immediately after delivery, and into the serum of the newborn 24 hours after birth. The Authors report the values and comment on them.

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INTRODUCTION

In reflux oesophagitis the therapeutic objectives are the inhibition of the secretion of gastric acid, of strengthening the defensive capacity of the lower oesophagus and of naturalising the reflux of the acid secreted ([1]).

When pregnancy occurs in women affected by reflux oesophagitis the same criteria remain and the inhibition of gastric secretion constitutes the basic therapeutic objective, nowadays easily obtained by means of drugs such as ranitidine antagonistic to the H_2 receptors ([2]).

Among many reports giving information concerning the use of this drug there has, on the contrary, been very little reference made in literature as to the use of ranitidine in pregnancy, therefore we record the results observed in a woman who had taken ranitidine regularly, at dose of 450 mg/die throughout the entire period of her pregnancy.

CLINICAL CASE

M. S., aged 39 (clinical chart no. 37/2.1.1988) referred to previous pregnancy in 1975, complicated from the beginning by irrepressable vomiting, pyrosis, epigastric and low retrosternal pain.

Her symptomology, soon became serious, because of the failure of the usual therapies, and alimentation then became almost exclusively parenteral. A moderate degree of megaloblastic anemia was present.

With a weight loss of about 20 kgs the patient gave birth to a female foetus weighing 2,200 grs, alive and viable.

After delivery the pyrosis, epigastralgia and low retrosternal pain continued. Having excluded cardiac disease by radiographic and gastroscopic examination and the histologic examination of bioptic fragments of the oesophagal mucosa, diagnosis was pronounced as "gastro-oesophagal reflux with chronic oesophagitis Grade II due to cardias incontinence".

Thanks to the advent of antisecretory drugs antagonistic to H_2 receptors of histamine, the patient had undergone first, treatment with cimetidine, then with ranitidine, reporting considerable benefit; numerous clinical and gastroscopic checks with biopsy in fact confirmed the improvement in the disease.

In the course of treatment with ranitidine for over 6 months (150+300 mg/die) (Zantac - Glaxo) the actual pregnancy occurred. The patient, very much wanting children and dreading the reappearance of the catastrophic symptomology which had characterised her first pregnancy, continued the treatment uninterruptedly, at the same dosage, although aware of the lack of precise knowledge as to the possible side-effects of the drug on the human foetus.

From amniocentesis at the 17th week of pregnancy, 4 hours after the intake of 150 mg of ranitidine, samples were taken of the amniotic fluid and of the maternal blood for the dosage of the drug.

The product of the conception proved to be normal kariotype 46 XX, the α-foetal protein within the norm, and absence of bilirubine in the amniotic fluid.

The echographic parameters of foetal growth showed increases within the norm; cardiotocographic tests from the 36th week expressed the wellbeing of the foetus. There was no evidence hyperemesis nor did any clinical symptoms of the oesophagitis reflux appear; weight increase was 13 kg; no signs of gestosis were manifested, and the usual haematochemical tests showed the normal values in pregnancy.

On admission to the hospital the amnioscopy revealed the presence of amniotic fluid stained with meconium, and we therefore proceeded with the monitorised induction of labour. The response was prompt, with rapid evolution and without any sign of acute foetal distress.

A female foetus was delivered spontaneously, with a turn of the umbilical cord round the neck, but alive and viable, weighing 4,020 grs with an Apgar score of 9-10: the afterbirth was spontaneous and complete with a placenta of 550 grs of normal appearance.

At the amniorrhexis amniotic fluid was not withdrawn for the dosage of ranitidine, as it was not considered suitable for research, being contaminated by the meconium; for this purpose, after delivery (which had taken place 5 hours after intake of 150 grs of ranitidine) we took samples from the maternal blood and from the umbilical cord; another blood sample was taken from the newborn 24 hours after birth.

The pediatric checks at 3-6-10 months were highly satisfactory for the wellbeing of the baby, who had only been breast-fed for the first week.

The various samples were serialised and frozen and the dosages of ranitidine were all carried out by the RIA method at the laboratories of the Institute of Legal Medecine and Insurance

at the University of Studies of Verona (Prof. M. Marigo) and resulted:

– serum of maternal blood at the 17th gestational week, 4 hours after taking 150 grs of the drug: 90 ng/ml;

– amniotic fluid at the 17th week, at the same time as the withdrawal of the maternal blood: 360 ng/ml;

– serum of maternal blood after delivery, 5 hours after taking 150 grs of the drug: 84 ng/ml;

– blood serum from the umbilical cord at the same time as that of the mother after delivery: 80 ng/ml;

– blood serum of the newborn 24 hours after birth, one and a half hours after the first breast feed: 160 ng/ml.

DISCUSSIONS AND CONCLUSIONS

Reports in literature on the use of ranitidine in the treatment of reflux oesophagitis in pregnancy are fragmentary and incomplete.

In 1982 the transplacentary passage of ranitidine was demonstrated in sheep, and a lower rate of the drug in the blood from the umbilical cord in respect to the manernal blood was noted [3].

Various studies on rats excluded the possibility that ranitidine has an antiandrogenic effect during its endouterine life, and adverse effects on subsequent sexual functions could also be excluded [4, 5, 6].

Rabbits given 400 mg/die of ranitidine developed no teratogenic effects, nor gave any signs of influence on weight, in the genital sphere, nor in ossification [7].

In the human stomach tissue obtained from the product of a therapeutic abortion at the 23th gestational week ranitidine proved to have been capable of influencing the activity of the glandular antihistamine receptors H_2 [8].

In 1983 a description referred to 3 cases of reflux oesophagitis in pregnancy treated with ranitidine, but the study was limited solely to the clinical observation of the wellbeing of the newborn [9].

In the case of the present study the seric concentration of ranitidine at the 17th gestational week and immediately after delivery, at 4 and 5 hours from the intake of 150 mg of the drug, was 90 and 84 ng/ml equal to the values reported in literature of other patients who had taken the same dose at the same distance of time [10].

In the amniotic fluid the values of ranitidine 4 hours after the intake of 150 mg was 360 ng/ml, the relation of amniotic fluid-maternal serum = about 4 : 1.

It was noted that after oral administration ranitidine had a different concentration in the various organic fluids examinable: in fact it was present in the maternal milk with a variable milk/plasma relation from 1 : 1 to 4 : 1, in the sperm with of 1 : 10 (after 2 hours) in the liquor of 1 : 30 (after 1½ hours) [10, 11].

The higher concentration of ranitidine in the amniotic fluid in respect to the maternal blood serum may be explined, in our opinion, by invoking two mechanisms; the first, of diffusion through the amniotic membrane (the same mechanism deputed to the regulation of the production and reabsorption of the amniotic fluid); the second, through the accumulation of the drug eliminated by the fetal kidneys; in fact the greater part of an oral dose of ranitidine is eliminated within 6 hours as ranitidine oxide, as a demethylised derivative, or as unmodified ranitidine [10, 11].

It would be interesting to know, on this subject, the values of ranitidine in specimens of amniotic fluid at different gestational stages, always at the same time after intake of the same dose of the drug.

The quantity of ranitidine present in the umbilical cord serum (80 ng/ml) proved to be almost the same as that met in the maternal serum (84 ng/ml). This datum is similar to that of Mihaly, reported in sheep and interpreted as an expression of the same concentration in both the maternal and fetal blood [3].

160 ng/ml proved to be the value of ranitidine in the newborn blood serum 24 hours after birth. The higher concentration in respect to the maternal serum may be interpreted by the presence of ranitidine in the milk (and, presumably, in the colostrum) in the milk/plasma relation from 1 : 1 to 4 : 1 ([10, 11]): in fact the newborn had just been at the mother's breast.

From the clinical point of view the wellbeing of the patient was remarkable inasmuch as she had been able to nourish herself normally, while the product of her conception was over average weight.

Taken as a whole the data derived from the case studied induces us to formulate the conclusion that ranitidine is a well-tolerated drug and has an excellent therapeutic effect on a pregnant woman affected by reflux oesophagitis, that it is a drug allowing for safe transplacentary passage with increase of concentration in the amniotic fluid, and that it is a drug which has neither teratogenic nor embryo-foetal toxic effects and does not induce harmful effects in the newborn. It is, however, desirable that other cases be reported in literature in order to amplify our knowledge on the subject.

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