Arab Gulf J.Scient. Res.. **12** (1), pp.133 - 140(1994)

Teratogenic and Toxic Effects of Hiconcil (Amoxicillin) on Mouse Foetuses

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ABSTRACT. Inbred normal adult CBA mice were used to investigate the possible teratogenic and other effects of Hiconcil (Amoxicillin) on foetuses of females treated intraperitoneally (ip) once each day from day 7 to 12 of pregnancy. The prenatal administration of Hiconcil at 500 or 650 mg/kg body weight resulted in both teratogenic and toxic effects on foetuses of treated mothers. Such effects comprised the development of abnormal hindlimbs and tails. However, the drug was safe to treated dams at all dose levels and at all times during gestation.

Hiconcil (Amoxicillin) is a broad spectrum semisynthetic pencillin that is effective against many Gram-positive and Gram-negative bacterial infections in man, such as skin infections, gonorrhea, urinary and respiratory tract infections and otitis media (Sutherland *et al.* 1972, Alergant 1973, Burns and Devitt 1974, Pankey 1974, Nolan and White 1978, Schawrtz *et al.* 1981, Savard-Fenton *et al.* 1982, Avner *et al.* 1983, Stahl *et al.* 1984, Masterton *et al.* 1985, Gerstner *et al.* 1989 and Anon 1990). The drug has also been used in the treatment of various experimental infections in mice (Boon and Beale 1987, Beale *et al.* 1988. Gisby and Beale 1988, Gelber 1991 and Gisby *et al.* 1991).

Ideally, no drug should be given during pregnancy. However, there are situations when chemotherapy is obligatory during pregnancy, and antibiotics are commonly used in such situations. Hence, it is essential to determine the safety of such drugs both for the mother and developing offspring. The present study has been undertaken to evaluate the effects of various doses of Hiconcil (Amoxicillin) both on pregnant mice and on their foetuses.

Materials and Methods

Normal adult inbred CBA mice maintained within a closed colony system, were used. They were housed in plastic boxes in an environmentally controlled room with a light/dark cycle of 14/10 hrs. In each box, 3-5 nulliparous females were caged together with a single male.

The commencement of pregnancy was determined by the detection of vaginal plugs in mated females, and the day the plug was observed was designated as day 0 of gestation. On day 7 through day 12 of pregnancy, the females were injected once daily intraperitoneally (ip) with 300, 400, 500, or 650 mg/kg Hiconcil (Mead Johnson and Company, Evansville, Indiana, U.S.A.) in sterile normal saline. Control mice were injected with the corresponding volumes of sterile normal saline alone. On day 17 of pregnancy, the mice were killed by cervical dislocation and the number of live foetuses and resorptions was noted. Each foetus was then examined macroscopically both externally and internally for gross developmental abnormalities. Ten foetuses from each group were then cleared and stained according to the modification of Abou-Tarboush (1987) of the method of McLeod (1980) for skeletal examinations.

Data were statistically analysed using the student's t-test and a 2×2 contingency table ($\times^2$) for the actual numbers obtained (Sokal and Rohlf 1981).

Results

The effects of Hiconcil on foetuses obtained from the pregnant mice are shown in Table 1. The results of the comparisons between Hiconcil-treated and control groups showed that there were no significant differences between the Hiconcil-treated and the control groups in mean number of implantation sites, mean live litter size or mean live foetal body weight at all dose levels used (Table 1). However, treatment with the drug has significantly ($p<0.01$) increased the proportion of resorption at dose levels of 500 and 650 mg/kg. Moreover, the drug has also induced some defects in two foetuses obtained from dams treated at 500 and 650 mg/kg (Table 1). Such defects included abnormal hindlimbs and tails together with reduction in body weight. Two types of tail abnormalities were observed in both defected foetuses, including shortening of tail length with sharply tapered tips and U-shaped bending of the tail. Moreover, backward bending of hindlimbs was also observed in both defected foetuses (Figs. 1-2). The mean body weight of abnormal foetuses was 0.42 ± 0.01 g, that of normal controls was 0.84 ± 0.03, the difference in weight is significant at $p<0.001$.

Table 1. Effects of various dose levels of Hiconcil on foetuses taken on day 17 of pregnancy in CBA mice

Hiconcil dose (mg/kg)	No.of females	No.of implantation sites (Mean±S.E.)	No.of Live foetuses (Mean±S.E.)	Resorption (%)	Live foetal body wt. (g) (Mean±S.E.)	Abnormalities observed
Control	20	6.50±0.36	6.50±0.36	0(0.00)	0.84±0.03	None
300	10	6.70±0.52	6.50±0.48	2(2.99)	0.85±0.02	None
400	20	6.75±0.37	6.50±0.36	5(3.70)	0.84±0.02	None
500	20	7.30±0.38	6.70±0.55	12(8.21)*	0.79±0.02	1 abn. foetus
650	20	6.80±0.52	6.15±0.57	13(9.56)*	0.83±0.03	1 abn. foetus

* Differences in resorption are statistically significant from the controls at $p<0.01$

Fig. 1. Foetuses obtained on day 17 of pregnancy from treated dams (500 mg/kg Hiconcil) and from controls.

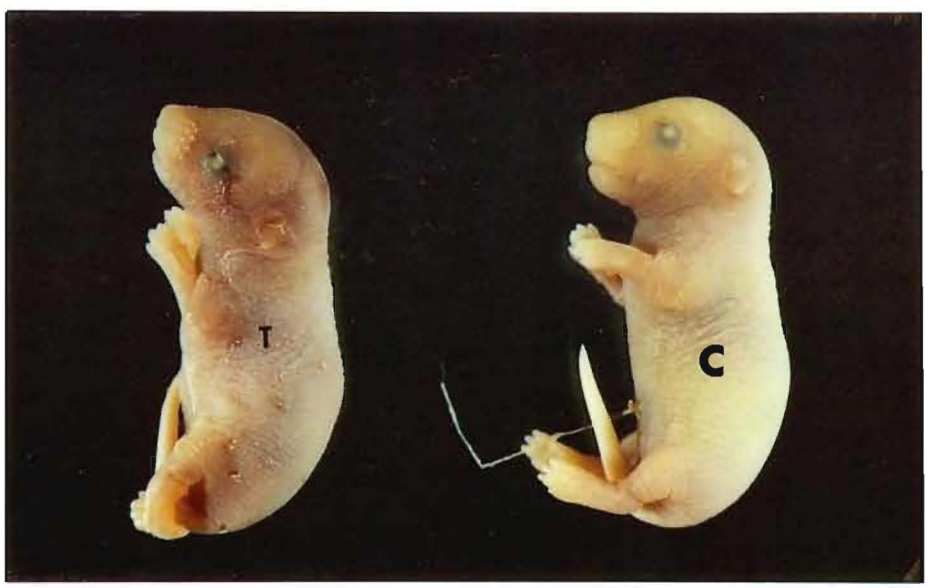

Fig. 2. Foetuses obtained on day 17 of pregnancy from treated dams (650 mg/kg Hiconcil) and from controls.

C = control T = treated

Discussion

The present study has demonstrated teratogenic and toxic effects of Hiconcil on developing mouse embryos whose mothers were treated with 500 and 650 mg/kg body weight of the drug during organogenesis. However, the present results are very much different from the general norm that penicillins, as a class, are safe throughout pregnancy in humans (Weistein 1975, Weistein 1979, Berkowitz *et al.* 1981, Schwartz 1981 and Briggs *et al.* 1986). This could well be due to the time of drug administration or to the species genetic differences or to both. However, Masterton *et al.* (1985) and Gerstner *et al.* (1989) have reported that the drug is effective and safe even at a single-dose of 3g or a 4-day course of 3 doses of 750 mg amoxicillin when given at a mean gestational age of 25 weeks. Moreover, the treated mouse dams were not obviously affected by the drug at any dose level used during any time of pregnancy.

It is apparent from the present study that Hiconcil has possible teratogenic and toxic effects on foetuses whose mothers were treated with high doses of the drug during organogenesis and should be avoided,if possible,during the first 10weeks of gestation in humans.

Acknowledgements

The author extends deep appreciation to Professor Dr.Hussin S. Hussein and to Mr. Saud N. Masoud for their valuable suggestions and assistance and to Mr. Ahmed Fath Al-Bab for typing the manuscript.

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(Received 25/11/1992;
in revised form 22/12/1993)

التأثيرات التشويهية والسامة لعقار الهايكونسيل (الأموكسيسيلين) على أجنة فئران التجارب

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استعملت في هذه الدراسة حيوانات طبيعية يافعة من فئران التجارب التي تنتمي للسلالة النقية المعروفة باسم CBA لدراسة احتمال حدوث تشوهات خلقية أو سامة نتيجة لاستعمال عقار الهايكونسيل (أموكسيسيلين) على الأجنة التي حقنت امهاتها بالجرعات ٣٠٠، ٤٠٠، ٥٠٠ أو ٦٥٠ مغم/كغم من وزن الجسم عند الحقن وخلال الفترة من اليوم السابع إلى اليوم الثاني عشر من الحمل. ولقد كان الحقن مرة واحدة يومياً. هذا وقد أوضحت نتائج هذه الدراسة أن حقن هذا العقار للأمهات خلال الفترة المشار إليها وبالجرعة ٥٠٠ أو ٦٥٠ مغم/كغم من وزن الجسم له تأثيراً مشوهاً على الأجنة المتحصل عليها من الامهات المعالجة.

كما أوضحت نتائج هذه الدراسة أن حقن هذا العقار قد أدى إلى زيادة ذات دلالة معنوية في نسبة امتصاص الأجنة (Resorption) في الامهات المعالجة عند الجرعة ٥٠٠ أو ٦٥٠ مغم/كغم فقط إلا أنه ليس لهذا العقار أية تأثيرات

ضارة على الأمهات المعالجة بأي من الجرعات المستخدمة في أي وقت خلال فترة الحمل.

من الواضح في هذه الدراسة أن لعقار الهايكونسيل تأثيراً مشوهاً وساماً على الاجنة المتحصل عليها من أمهات عولجت بجرعات عالية من هذا العقار خلال فترة تكون الاعضاء، لذا ينصح بتجنب استخدام هذا العقار من قبل النساء خلال الاسابيع العشرة الأولى من فترة الحمل.