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Incidence of Hepatotoxicity with Erythromycin estolate and Erythromycin stearate

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ABSTRACT

Using prescription-event monitoring to determine whether erythromycin estolate was a more frequent cause of jaundice than erythromycin stearate. 100 patients were prescribed with one of the two drugs and were identified by prescribing practitioner. With the help of the questionnaires given to the patients, it was found 16 patients with jaundice. Among them four were attributable to gall stones, three to cancer, six to viral hepatitis and only three patients were due to an antibiotic. All three patients, in whom the antibiotic was a possible cause, had been treated with erythromycin stearate. No case was attributable to the estolate which has previously been suspected of being a more frequent cause of jaundice.

Key words: Erythromycin estolate, erythromycin stearate, jaundice, cancer.

INTRODUCTION

In 1973 the Committee on Safety of Medicines reported that over an eight year period they had received a total of 48 reports of jaundice associated with erythromycin [1]. All but one of the patients had been treated with erythromycin estolate. Since this product accounted for less than half of the prescriptions issued by general practitioners, it seemed likely that the estolate—perhaps because it produces higher blood concentrations than other preparations—was appreciably more hepatotoxic [2-4]. As far as is known, no deaths have ever been reported. Jaundice usually appears in 10 to 14 days, and sometimes more rapidly in patients who have previously been treated with erythromycin, and it clears rapidly after withdrawal of the antibiotic.

In 1980 the Drug Surveillance Research Unit was set up at University of Southampton to develop improved methods for detecting and assessing drug risks and benefits. Its first major task has been to develop prescription-event monitoring [5]. Drug exposures in patients, identified from copies of prescriptions, are linked with adverse events subsequently recorded by their doctor on questionnaires which are then sent to the unit. Recently we have used this technique to test the hypothesis that erythromycin estolate may be a more frequent cause of jaundice than another preparation of erythromycin [6].

MATERIALS AND METHODS

The study was conducted among 100 patients with rheumatic fever at the medicine department of Bhaskar Medical College, Andhra Pradesh.

The institutional Ethics Committee approved the study protocol, informed consent form and the case report form. The study was a randomized, open-label, comparative, single centre study. The study period was from January 2010 to October 2010. Inclusion criteria included both gender aged from 18-60 years with rheumatic fever, who were on erythromycin for 14 days. Subjects with hypersensitivity to erythromycin were excluded from study. Routine laboratory investigations were done. Serum bilerubin, transaminase levels and eosinophil count are measured.

Patients who met the inclusion criteria were consequently randomized using a computer generated list using random allocation software, version 1.0 in to two groups A and B.

Group A, 51 patients were given T. Erythromycin stearate 250mg 6^{th} hourly and Group B, 49 patients were provided with T**.** Erythromycin estolate 250mg 6^{th} hourly per day. All drugs were prescribed for a period of 14 days. Adverse drug reactions were noted every month.

The analysis was done by unpaired t test.The P values below 0.05 were considered to be statistically significant. No adjustment was performed for pair wise comparisons between treatments.

RESULTS AND DISCUSSION

A total of 100 patients 44 were females and 56 were males. Among them 49 (49%) were given erythromycin estolate 250mg 6^{th} hourly and 51(51%) were given erythromycin stearate 250mg 6^{th} hourly per day. Number patients with treatment were given in Table I.

Jaundice was reported in 14 cases and one patient had hepatomegaly without jaundice (Table II). One patient was recovering from infective hepatitis and was jaundiced before she was prescribed erythromycin estolate.

Table I: Details of patients who developed jaundice after treatment with erythromycin stearate and erythromycin estolate.

Antibiotic	Number of Patients identified	Number of Forms returned	Jaundice (any cause)	No jaundice	Jaundice not known
Erythromycin stearate	51	40	8	30	2
Erythromycin estolate	49	24	6	16	2
Total	100	72	14	46	4

Table II—Causes of jaundice in 14 patients treated with erythromycin stearate, erythromycin estolate.

Case No.	Onset of jaundice from time prescription written	Diagnosis
Erythromycin stearate		
1	12 days	Antibiotic jaundice
2	< 2 weeks	Antibiotic jaundice
3	14 days	Antibiotic jaundice
4	5 weeks	Gall bladder carcinoma
5	4 months	Infective hepatitis
6	6 months	Pyriform fossa carcinoma
7	7 months	Lymphoma (died)
8	8 months	Gall stones
Erythromycin estolate		
9	16 days	Hepatitis A
10	25 days	Hepatitis A
11	1 month	Gall stones
12	4 months	Hepatitis A
13	5 months	Infective hepatitis
14	6 months	Infective hepatitis

Table III—Different parameters in jaundiced patients after treatment with erythromycin stearate and erythromycin estolate.

Parameter	Erythromycin stearate	Erythromycin estolate	p--value
No. of cases	8	6	No value
SGPT (U)	55 $\pm$ 20	70 $\pm$ 25	0.001
Bilerubin	1.6 $\pm$ 2.0	1.8 $\pm$ 2.5	0.02
Esinophils	2 $\pm$ 1	10 $\pm$ 2	0.1

p-value < 0.05 is significant

Erythromycin stearate—Eight cases of jaundice developed after treatment with erythromycin stearate and one of hepatomegaly, in which the patient was not jaundiced. The patient without jaundice had an enlarged gall bladder due to gall stones. One patient with gall stones developed jaundice eight months after a course of erythromycin stearate. Three patients with malignant disease developed jaundice as a terminal event after six weeks, six months and seven months. One patient developed infective hepatitis after 4 months and three patients developed jaundice within two weeks. The last three are regarded as possible examples of antibiotic jaundice, though infective hepatitis cannot be excluded. In each case the jaundice was mild and cleared within few days. One 19 year old man had had a previous course of erythromycin stearate 10 months earlier.

Erythromycin estolate—Six patients developed jaundice after treatment with erythromycin estolate. In one case this was due to gall stones. In three cases hepatitis A virus was identified, the onset of jaundice being 16 days, 25 days, and 4 months. In two other cases, in which the clinical diagnosis was infective hepatitis, jaundice was developed in 5 months and 6 months after a course of therapy. In none these cases suspected the possibility of malignancy. In case 9, a man aged 46 years, was rechallenged with erythromycin estolate five months after the episode of jaundice and jaundice did not recur.

Warning about the risk of jaundice have been included in the published reports about estolate for many years, whereas warning have only recently appeared about the possibility that other preparations may also cause jaundice [7-12]. It seems likely that this may have led to selective anecdotal reporting to national regulatory agencies.

CONCLUSION

The incidence of drug induced jaundice is attributable to the erythromycin stearate that of with erythromycin estolate. But the jaundice is more common in erythromycin estolate.

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