Clinical Topics

Erythromycin estolate and jaundice

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Abstract

Using prescription-event monitoring to determine whether erythromycin estolate was a more frequent cause of jaundice than erythromycin stearate or tetracycline 12 208 patients, for whom 5343 doctors had prescribed one of the three drugs, were identified by the Prescription Pricing Authority. Of the questionnaires sent to general practitioners about the possible occurrence of jaundice, 76% were returned. There were 16 reports of jaundice, of which four were attributable to gall stones, three to cancer, six to viral hepatitis, and only three were possibly related 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 had previously been suspected of being a more frequent cause of jaundice. Although the incidence is unknown, it is very unlikely to be more than one in 1000.

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. 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 the 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.² Drug exposures in patients, identified from copies of prescriptions, are linked with adverse events subsequently recorded by their doctors on questionnaires (green forms) 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.

Materials and methods

Prescriptions for erythromycin estolate (Ilosone, Dista), written in England between 1 January and 28 February 1982, were photocopied by the Prescription Pricing Authority and passed to the Drug Surveillance Research Unit. Prescriptions for the much more widely used erythromycin stearate (Erythrocin, Abbott) and tetracycline (Achromycin, Lederle) were also obtained from a random sample of 19 of the 90 family practitioner committee areas in England to provide a comparison. The Erythrocin sample was collected during the month of January and the Achromycin sample in February. When a doctor uses the approved name of a drug on his prescription, it is only possible to identify which formulation the patient received if the pharmacist has annotated the prescription with the name of the product that was dispensed. Our selection of cases was, therefore, restricted to patients whose treatment has been identified precisely by means of the brand name.

Questionnaires were prepared for up to six patients in any one doctor's practice. The patients were identified simply by a capital letter and the photocopies of the prescriptions, marked with the same capital letter, were pinned to the questionnaires. No copies were retained by the unit and the general practitioners were asked to retain the prescriptions for a few weeks as a means of identification in case further information should be needed. Practitioners were asked to note whether the prescriptions were the first to be issued during the present illness and whether or not the patients had developed jaundice.

Results

A total of 5343 green forms were dispatched at the end of the last week in October 1982, relating to 12 208 patients; 5386 (44%) had received a prescription for erythromycin stearate, 4373 (36%) for erythromycin estolate, and 2449 (20%) for tetracycline. Of the green forms 4042 (76%) had been returned by 13 January 1983, giving information on 9236 (76%) of the patients (table I). The question about jaundice was not answered for 624 (7%) of the patients, most commonly because the patients had left the practice.

Jaundice was reported in 18 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. Another patient had developed jaundice, which was thought to have been due to glandular fever, after an earlier exposure to tetracycline in 1978 and jaundice did not recur

TABLE I—Details of patients who developed jaundice after treatment with erythromycin stearate, erythromycin estolate, and tetracycline

Antibiotic	No of patients identified	No of forms returned	No of reports of:		
			Jaundice (any cause)	No jaundice	Jaundice not known (or no answer)
Erythromycin stearate	5386	4095	8	3811	276
Erythromycin estolate	4373	3314	6	3084	224
Tetracycline	2449	1827	2	1701	124
Total	12208	9236	16	8596	624

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when this antibiotic was used again in 1982. These three cases are not included in table II. In all these cases a letter was written to the general practitioner requesting further information. This was obtained in every case, and in none was the final diagnosis modified (table II). There were five men and 12 women, whose ages ranged from 15 to 81 years.

TABLE II—Causes of jaundice in 16 patients treated with erythromycin stearate, erythromycin estolate, or tetracycline

Case No	Onset of jaundice from time prescription written	Diagnosis
<i>Erythromycin stearate</i>		
1	4 months	Infective hepatitis
2	14 days	? Antibiotic jaundice
3	6 months	Carcinoma, pyriform fossa (died)
4	6 weeks	Carcinoma, gall bladder (died)
5	7 months	Lymphoma (died)
6	12 days	? Antibiotic jaundice
7	8 months	Cholelithiasis
8	<2 weeks	? Antibiotic jaundice
<i>Erythromycin estolate</i>		
9	4 months	Hepatitis A
10	1 month	Cholelithiasis
11	25 days	Hepatitis A
12	16 days	Hepatitis A
13	5 months	Infective hepatitis
14	6 months	Infective hepatitis
<i>Tetracycline</i>		
15	Uncertain	Cholelithiasis
16	7 months	Cholelithiasis

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 four 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 a 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 cholelithiasis. In three cases hepatitis A virus was identified, the onset of jaundice being 16 days, 25 days, and four months. In two other cases, in which the clinical diagnosis was infective hepatitis, jaundice had developed three months and six months after a course of Ilosone. In none of these cases is Ilosone suspected as a possible cause. The patient in case 12, a man aged 46 years, was rechallenged with erythromycin estolate five months after the episode of jaundice and the jaundice did not recur.

Tetracycline—In one of the two patients treated with tetracycline,

jaundice was due to gall stone fragments in the common bile duct. In the second patient, who developed jaundice seven months after a course of treatment with tetracycline, no stones were found at operation and a liver biopsy showed changes of mild hepatitis. Neither case is attributable to the antibiotic.

Discussion

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

The incidence of jaundice attributable to the estolate has been variously estimated as between 2% and 4%.³ The fact that none of more than 3000 patients treated with the estolate developed jaundice which was attributable to the drug suggests that its incidence is much lower. Our results suggest that it is very unlikely to be more than one per 1000 and probably a good deal lower. We hope that it may be possible to study a much larger series of patients at a future date, but in the meantime we see no reason for special concern about the safety of this antibiotic.

The most striking result from this investigation was the high level of cooperation by general practitioners. The green forms often included words of encouragement and support for the new method and many doctors also remarked about the extreme rarity, in their experience, of jaundice with any preparation of erythromycin. The response of 76% augurs well for the future of prescription-event monitoring as an effective method for generating and testing hypotheses about drug safety and efficacy.

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References

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- 2 Inman WHW. Post-marketing surveillance of adverse drugs in general practice. II Prescription-event monitoring at the University of Southampton. *Br Med J* 1981;282:1216.
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What investigations should be done for azoospermia and what treatment is advised?

Azoospermia or complete absence of sperm in the ejaculate is due either to failure of production of sperm or to complete obstruction to the passage of sperm produced by the testes. The aetiology in both groups is usually congenital rather than acquired. It is possible for a man to be born without a germinal epithelium, the so called Sertoli cell only syndrome. Leydig cells are present, usually in normal quantities, and hence the serum luteinising hormone and testosterone concentrations are normal and secondary sexual characteristics well developed. The testicles are usually small and soft, and the serum follicle stimulating phenomenon concentration appreciably raised. Occasionally the germinal epithelium is destroyed, as in bilateral torsion or mumps orchitis, when subsequent atrophy may occur. The congenital causes of obstructive azoospermia include varying degrees of aplasia of the epididymis and absent or atretic vasa deferentia. Acquired causes of obstruction are inflammatory—for instance, genitourinary tuberculosis, severe bilateral epididymitis, gonococcal strictures of the vasa, or traumatic (in particular, surgical damage to either the vas or epididymis). To differentiate between an obstructive

cause for azoospermia and an absent germinal epithelium, testicular biopsy is necessary. If there is no germinal epithelium then no treatment is available. If the cause for azoospermia is obstruction then surgery may be helpful. The sites of obstruction in the vasa deferentia can be located by intraoperative vasography, the strictured segments excised, and end to end vasovasostomy performed. If the vasa are patent and the caput epididymis seen to be tensely distended by dilated tubules full of sperm, then the operation of side to side vaso-epididymostomy is indicated. The results of surgery are reasonable in acquired epididymal obstruction but disappointing for congenital obstruction.—J C GINGELL, consultant urologist, Bristol.

Do beta-blockers adversely affect visual acuity in elderly people?

I am unaware of any work done on this question. A reduction in visual acuity would not be unexpected. In view, however, of the large spread of normal data in higher age groups a carefully controlled study would be needed to clinch the matter.—R A WEALE, professor of visual science, London.