Risk factors for development of flucloxacillin associated jaundice

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Abstract

Objectives—To identify risk factors predisposing to the development of flucloxacillin associated jaundice.

Design—Case-control study. Medical records of cases and controls were reviewed and information recorded on standard data collection forms.

Setting—Alfred Hospital recruiting subjects from Melbourne, Sydney, and Brisbane.

Subjects—Cases were defined as patients who had developed jaundice within eight weeks of stopping flucloxacillin, biochemical test results suggesting cholestasis, normal calibre bile ducts, and not been taking recognised hepatotoxic drugs. 51 of the 53 patients referred were included in the study. Four controls for each case were randomly selected from the patient register of the prescribing doctor. These were defined as patients who had been prescribed flucloxacillin without developing jaundice.

Main outcome measures—Demographic characteristics, medical history, indication for flucloxacillin, dose, route and duration of treatment, other drugs, smoking, and previous drug allergies or use of flucloxacillin.

Results—Increasing age and a prolonged duration of flucloxacillin treatment were found to be risk factors for the development of jaundice. Patients aged over 55 years had an odds ratio of 18.61 (95% confidence interval 5.16–67.17) compared with patients under 30. The odds ratio for patients prescribed flucloxacillin for over 14 days was 7.13 (2.90 to 17.58) compared with patients treated for 14 days or less. Dose and route of administration were not related to the risk of jaundice.

Conclusions—Older patients and those receiving flucloxacillin for longer than two weeks are at a substantially greater risk of jaundice. Careful consideration of the risk-benefit ratio is required when flucloxacillin is used in these settings.

Introduction

Flucloxacillin is a semisynthetic penicillin that is useful for treating infections with methicillin sensitive staphylococci that produce penicillinase. Cholestatic jaundice associated with the use of this drug is rare but often severe. Jaundice often persists for more than three months and abnormal liver function may persist for 12 months or more.^{1,2}

Damage to the liver associated with flucloxacillin was first reported in 1982.³ Since then further cases have been reported in Australia (131 cases), Sweden (48 cases), and the United Kingdom (21 cases).^{4,5} In Australia the incidence of liver damage has paralleled the increased use of flucloxacillin. We conducted a retrospective case-control study to determine whether any defined group of patients is at increased risk of developing flucloxacillin associated jaundice.

Methods

A case definition was established after reviewing previous reports to the Australian Adverse Drug Reaction Advisory Committee. Cases were eligible for inclusion in the study if they met the following criteria: jaundice occurred within eight weeks of the patient stopping flucloxacillin, results of liver function tests suggested cholestasis, bile ducts were normal diameter by ultrasonography or endoscopic retrograde cholangiopancreatography, patient had no other recognised causes of jaundice of hepatotoxic drugs.

Cases were recruited to the study from two sources. The first was the adverse drug reactions section of the Commonwealth (Australian) Department of Health, Housing, and Community Services. This section receives spontaneous reports of adverse drug reactions from hospitals, doctors, and pharmacists. An algorithm is used to classify reports according to the likely mechanism (idiosyncrasy, pharmacological action, etc) and the likelihood of the specified drug having caused the adverse reaction—that is, certain, probable, possible, and unlikely. Cases classified as unlikely were not used in this study. All drugs prescribed within an appropriate time frame are considered as possible causes with the term “sole suspected drug” being confined to cases where only a single drug has been prescribed before the onset of the suspected reaction.

Staff from the adverse drug reaction section wrote to 82 Australian doctors who had reported cases, requesting permission to pass their names on to the study centre. Fifty one doctors responded and 26 were selected because they lived within a convenient distance from the study centre (that is, in metropolitan Melbourne, Sydney, or Brisbane and the state of Victoria). These doctors were then contacted and asked to obtain permission for the study to contact the doctor who prescribed flucloxacillin to the patient. Twenty six prescribing doctors were subsequently contacted and all made their records available to the investigation. Twenty four of the patients identified fulfilled the inclusion criteria for the study.

We also obtained cases from a specifically established surveillance programme operated by hepatologists in Melbourne, a city of 3 million people. Between October 1991 and March 1992 27 new cases of jaundice meeting the case definition were identified and included in the case series. The prescribing doctor was then identified and the above protocol followed.

When the case was prescribed flucloxacillin by a private medical practitioner, the study's research nurse attended the practitioner's office and selected controls from the patient record system. This was done by progressing forwards (alphabetically) from the case record until four patients who had been prescribed flucloxacillin without developing jaundice had been identified. When the prescribing doctor was employed by a hospital a similar procedure was conducted with hospital records.

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Information from the medical record was entered on to a standard data extraction form by a research nurse. Care was taken to exclude information recorded after the time the flucloxacillin was prescribed. This was to avoid bias resulting from additional information being sought about potential hepatotoxins (for example, alcohol) once jaundice had been diagnosed.

Information was recorded about demography, medical history, indication for flucloxacillin, dose, route and duration of treatment, other treatments, smoking, and previous drug allergies or use of flucloxacillin.

After being checked for completeness, the data were entered on to a relational database and analysed with the EGRET statistical software package. Conditional logistic regression of the cases and matched controls was used to generate odds ratios for factors potentially associated with the development of jaundice. Potential interactions between factors were studied by including

TABLE I—Characteristics of patients with flucloxacillin associated jaundice. Values are means unless stated otherwise

Variable	All cases (n=51)	Patients identified by ADRAC (n=24)	Patients identified by surveillance programme (n=27)	Patients in whom flucloxacillin was sole suspected drug (n=10)
Mean age (years)	60.1	55.7	63.7	55.9
M:F	22:29	9:15	13:14	4:6
Aspartate aminotransferase*	4.4	4.2	4.6	3.7
Alkaline phosphatase*	5.2	4.8	5.7	4.1
γ Glutamyltransferase*	8.5	8.9	8.1	10
Bilirubin*	10	11	8.8	9.4

*Enzyme and bilirubin values are given as a factor times the upper limit of normal concentration. Upper normal limits are 35 U/l for aspartate aminotransferase, 120 U/l for alkaline phosphatase, 30 U/l for γ glutamyltransferase, and 18 μmol/l for bilirubin.

ADRAC=Australian Drug Reactions Advisory Committee.

TABLE II—Crude odds ratios for developing flucloxacillin associated jaundice

Variable	No of cases (n=51)	No of controls (n=199)	Odds ratio (95% confidence interval)*
Age (years): Mean‡	59.8	38.3	—
< 30	3	84	1.00
30–55	17	58	7.56 (2.14 to 26.67)
> 55	31	54	18.61 (5.16 to 67.17)
Duration of treatment (days):‡			
≤ 14	32	180	1.00
> 14	18	19	7.13 (2.90 to 17.58)
Mean (SD)	14.0 (11.3)	8.1 (5.5)	
Previous serious illness or disease:			
No	20	131	1.00
Yes	31	68	2.90 (1.5 to 5.9)
Concomitant drugs:			
No	11	87	1.00
Yes	40	112	2.80 (1.3 to 6.2)
Sex:			
M	29	86	1.00
F	22	113	0.55 (0.28 to 1.06)
Mean (SD) dose (g):‡	2.57 (1.63)	2.18 (1.53)	p=0.16†
Indication for flucloxacillin:‡			
Prophylaxis	14	50	1.00
Infection	37	145	0.93 (0.43 to 1.94)
Smoker:‡			
No	17	67	1.00
Yes	6	32	0.76 (0.28 to 2.07)
Drinks alcohol‡			
No	6	36	1.00
Yes	13	34	2.15 (0.64 to 7.26)
Excess alcohol intake‡			
No	19	67	1.00
Yes	0	3	0.00 (0.00 to 78.00)
Allergy to penicillin‡			
No	43	168	1.00
Yes	1	4	0.00 (0.00 to 4.00)
Previous flucloxacillin‡			
No	20	76	1.00
Yes	3	21	0.64 (0.16 to 2.49)
General anaesthetic‡			
No	45	177	1.00
Yes	5	21	0.93 (0.28 to 3.07)
Route of administration			
Oral	40	154	1.00
Intravenous	6	16	1.40 (0.40 to 4.94)
Both	5	29	0.69 (0.19 to 2.43)

*Estimates of odds ratios for cases and matched controls obtained by conditional logistic regression.

†Two tailed Student's *t* test.

‡Data not available on all patients.

TABLE III—Medical history of cases and controls taking flucloxacillin

Type of medical condition	No (%) of cases (n=51)	No (%) of controls (n=199)
Cardiac	23 (45)	53 (27)
Respiratory	8 (16)	12 (6)
Arthritis	8 (16)	22 (11)
Hepatitis	3 (6)	3 (2)
Gastrointestinal	4 (8)	12 (6)
Renal	4 (8)	3 (2)
Cancer	3 (6)	6 (3)
Dermatological	4 (8)	1 (1)
Neurological	3 (6)	10 (5)
Miscellaneous	6 (12)	10 (5)

TABLE IV—Drugs taken concurrently with flucloxacillin

Drugs	No (%) of cases (n=51)	No (%) of controls (n=199)
Phenoxymethylpenicillin	10 (20)	16 (8)
Amiloride plus hydrochlorothiazide	5 (10)	4 (2)
Heparin sodium	7 (14)	9 (5)
Digoxin	5 (10)	5 (3)
Temazepam	7 (14)	17 (9)
Salbutamol	6 (12)	5 (3)
Potassium supplements	9 (18)	10 (5)
Paracetamol	10 (20)	29 (15)

Table includes only drugs taken by at least five patients.

the relevant interaction (that is, cross product) terms in the conditional logistic regression models.

The protocol was approved by the ethics committee at each of the Victorian hospitals that participated in the study. The study was conducted according to the guidelines for the protection of privacy approved by the Australian privacy commissioner.

Results

Fifty one cases of flucloxacillin associated jaundice were studied, 24 of which were identified through the Adverse Drug Reaction Advisory Committee and 27 through the surveillance programme in Melbourne. Sixteen of the patients had been prescribed flucloxacillin in hospital and the remainder had been prescribed the drug by a private doctor.

Table I gives the characteristics of the patients identified from the two sources and those of patients in whom flucloxacillin was the sole suspected drug. No differences were observed by analysis of variance and the cases were amalgamated to form a single series.

Table II shows the characteristics of the cases and controls and the crude measures of association. In general cases were older and had received flucloxacillin for longer. Cases were more likely to have taken other prescribed drugs and experienced multiple underlying illnesses. However, no specific drug or underlying condition occurred substantially more commonly in cases than in controls (tables III and IV).

Several of the factors associated with flucloxacillin jaundice were also likely to be associated with one another. Age was the strongest associated factor and duration of treatment was also associated with risk of jaundice. Medical history and taking of concomitant drugs were also significantly associated with the risk of jaundice, but these associations disappeared after controlling for age.

An examination of the joint effect of age and duration of treatment indicated a significant interaction ($p=0.046$) between the two effects (table V). Specifically, the effect of a longer duration of treatment was greater in the younger group (age ≤ 55) than the older group (age > 55).

Discussion

In Australia flucloxacillin is widely regarded as the best treatment for infections with methicillin sensitive

TABLE V—Combined effect of age and duration of treatment on risk of flucloxacillin associated jaundice

	No of cases (n=50)	No of controls (n=196)	Odds ratio (95% confidence interval)
Age ≤ 55 years:			
≤ 14 Days' treatment	12	133	1.0*
> 14 Days' treatment	8	9	13.3 (3.7 to 47.8)
Age > 55 years:			
≤ 14 Days' treatment	20	44	6.0 (2.4 to 15.1)
> 14 Days' treatment	10	10	17.0 (5.0 to 57.8)

*Reference group is age ≤ 55 years of age and duration of treatment of ≤ 14 days.

Staphylococcus aureus and *Staphylococcus epidermidis*. It has almost replaced cloxacillin since it was found to be better absorbed after oral administration and to produce higher and more prolonged blood antibiotic concentrations.⁶ Flucloxacillin's increasing use has been accompanied, since 1989, by a sharp increase in reports of severe and prolonged cholestatic jaundice, which has led to concern about the risk-benefit ratio for this drug. The condition has also been reported increasingly commonly in Sweden and to a lesser degree in the United Kingdom.⁴

We found that increasing age and prolonged duration of treatment are powerful risk factors for developing flucloxacillin associated jaundice. Concomitant drugs and previous serious illness were also associated but these reflected the older age of the cases and the relations disappeared once age was taken into account. There was no apparent relation with sex, route of administration, daily dose, or a history of penicillin allergy. The small size of the study did not allow precise estimation of the relative risk of jaundice for particular subgroups.

The study may have been affected by several types of bias. The cases probably represented an atypical subset of all patients with this condition because jaundice is more likely to be attributed to a drug if it is relatively severe and occurs soon after the drug is administered. However, this phenomenon would only affect our results if the factors associated with jaundice in unrecognised cases were different from those in the cases we studied.

Similarly, the controls were unlikely to be entirely representative of all subjects who received flucloxacillin without developing jaundice. Patients seen by the same prescribing doctor are a convenient control group but they may be more similar in terms of age, drug doses used, conditions treated, etc than would otherwise be expected. This effect would probably reduce the size of the odds ratios and thereby underestimate the strength of the relations observed.

Our findings are partly in keeping with those of Olsson *et al*, who studied 32 cases of flucloxacillin associated jaundice reported to the Swedish Adverse Drug Reactions Advisory Committee.⁵ Characteristics of these patients were compared with those of patients included in prescription sample surveys, which are regularly undertaken in Sweden. Patients developing jaundice were found to be older, to have received higher doses of flucloxacillin, and to be more likely to be female than those from the survey.

RISK-BENEFIT RATIO

The identification of subjects at increased risk of developing a serious adverse drug reaction can improve the risk-benefit ratio of drug treatment. For example, the finding that old age was a powerful risk factor for neutropenia after treatment with mianserin led to a

warning about using this drug in elderly patients.⁷ However, the drug is still used widely in young people, where its low risk following overdose is an advantage. A similar strategy has been used with cotrimoxazole.

The percentage of cases of flucloxacillin associated jaundice attributable to advanced age can be determined by the epidemiological formula for population attributable risk. In 1991 in Australia 16% of community prescriptions for flucloxacillin were for patients aged over 55 years (International Medical Statistics data, personal communication). The odds ratio for patients aged over 55 years (compared with those younger than 55) was 4.2. From these data it can be determined that one third of the cases which occurred outside hospital could be avoided if the drug were to be used exclusively in subjects under 55 years.

Flucloxacillin is a member of the isoxazolyl group of penicillins, which also includes cloxacillin, oxacillin, and dicloxacillin. In the United States, where flucloxacillin is not approved for use, no problem of similar size has been identified with the other isoxazolyl penicillins. Throughout the United States dicloxacillin (and to a lesser extent cloxacillin) is used for oral antistaphylococcal therapy while oxacillin is commonly used for parenteral treatment (United States Food and Drug Administration, personal communication). Each of these drugs has been reported to cause some degree of hepatotoxicity but their relative incidence is not clear. Olsson *et al* related the number of spontaneous reports of hepatotoxicity received by Swedish authorities to a measure of use (defined daily doses) and found a ratio of 1.9 cases per million defined daily doses with flucloxacillin, 1.3 with cloxacillin, and 0.75 with dicloxacillin.⁵ However, they gave little information about the severity of the hepatitis caused by each drug. Although it seems unlikely that these drugs could be associated with a hepatitis as severe as that associated with flucloxacillin, the possibility remains that the reaction has not been recognised.

In summary, this study identified increasing age and duration of treatment as powerful risk factors for the development of flucloxacillin associated jaundice. Because of the severity of this condition the drug should be prescribed only where there is a clear indication for antibiotics. When an older patient requires treatment or when prolonged treatment is likely, an alternative drug such as cloxacillin, oxacillin, or dicloxacillin should be considered. Careful prospective studies will be necessary to establish the hepatic risk associated with these drugs.

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