Flucloxacillin associated cholestatic hepatitis
An Australian and Swedish epidemic?

Received: 25 January 1995 / Accepted in received form: 19 April 1995

Abstract The clinico-pathological entity of flucloxacillin-associated cholestatic hepatitis is described and the recognition and documentation of cholestasis associated with flucloxacillin and with related isoxazolyl-penicillins (cloxacillin, dicloxacillin) is examined on an international basis, with particular reference to Australia. Data were obtained from the literature, from the Australian adverse drug reaction monitoring agency and from the Collaborative Centre for International Drug Monitoring (World Health Organisation) in Sweden. Approximately 600 cases of flucloxacillin-associated cholestatic hepatitis were collected, as well as 164 cases associated with other isoxazolyl penicillins.

Jaundice and pruritus may first appear several weeks after administration of the drug has ceased and typically are severe and protracted. Liver tests may be abnormal for months after symptomatic recovery. Death is uncommon. Liver pathology shows centrilobular bile stasis with portal tract inflammation and variable loss of bile ducts. Approximately 1 in 15,000 users of flucloxacillin will develop the reaction. Increasing age (> 55 years) and prolonged intake (> 14 days) are particular risk factors. Cholestasis associated with cloxacin/dicloxacillin appears to be similar in nature but is less well defined. Recognition and reporting of the reaction have been uncommon in the United Kingdom inter alia and high in Sweden and Australia, although estimates of risk have been similar. In Australia, the remarkably high rate of reports appears to be the result of sustained publicity for the reaction. There is only a trickle of reports of cholestatic hepatitis in association with the use of cloxacillin and dicloxacillin from the USA and Canada. The high level of awareness of the reaction and consequential regulatory action so far have not resulted in a diminution of its occurrence in Australia.

Key words Isoxazolyl penicillins, Adverse drug reaction reporting; jaundice, drug-induced hepatitis, flucloxacillin, dicloxacillin

In the broad spectrum of adverse drug reactions to penicillins, hepatic reactions have not been prominent [1], and their occurrence has been regarded as sufficiently unusual to warrant publication of individual case reports. The majority of such case reports have concerned the semi-synthetic, penicillinase-resistant, isoxazolyl-penicillins, oxacillin, cloxacin and dicloxacillin [2-6]. However, during the last decade, and particularly since 1989, a number of reports described multiple cases of hepatic reactions associated with the use of flucloxacillin [7-11]. Between 1989 and 1992 the adverse drug reaction (ADR) monitoring agencies of Australia, Sweden and the United Kingdom published warnings about these reactions [12-15], which were usually cholestatic in nature, and were characterised by their severity and persistence. In response to a continuing flow of reports, the Australian ADR agency published further analyses of morbidity [16, 17, 19] and mortality [20] associated with the reaction.

With the exception of the USA and Canada, flucloxacillin is the anti-staphylococcal agent of choice in most countries. It is notable, therefore, that almost 90% of reports of flucloxacillin jaundice submitted to the WHO Collaborating Centre for International
Drug Monitoring, by October 1993 had been sent by Australia and Sweden, two of its smaller affiliated countries (in terms of population). This paper describes the nature of the reaction and examines possible reasons for the discrepant rates of its reporting in different countries.

**Materials and methods**

Three major sources of information have been utilised. The first is the published literature which provides data on the clinical features and course of the reaction, and on its pathology, pathogenesis, frequency and possible risk factors. The second source is the spontaneous reporting system of ADR’s in Australia which is the largest single source of reports of flucloxacillin-associated hepatitis. The third source is the data collected by the World Health Organisation’s Collaborative Centre for International Drug Monitoring in Sweden. This Centre collates ADR data submitted by co-operating countries throughout the world. Examination of this information provides a perspective on the reporting pattern of suspected cases of flucloxacillin-associated hepatitis in different countries.

**The reaction**

**Clinical features**

The first case of flucloxacillin induced hepatitis was reported in 1982. The authors described a mild elevation in aminotransferases, without jaundice [21]. Three years later, two reports described cholestatic hepatitis [7, 22] in three patients, with moderate to severe intrahepatic cholestasis and with portal inflammation. To date, 30 individual case reports of cholestasis have been described in twelve publications [7-11, 17, 18, 21-24]. Most of the patients were women (77%) and the mean age of onset was 61. The predominant symptoms reported were jaundice (95%) and pruritus (77%). Other symptoms included dark urine, pale faeces, nausea, abdominal pain, fever, vomiting, lehargy, anorexia and weight loss. The most distressing symptom was usually pruritus. It was typically refractory to treatment with prednisone, cholestyramine, antihistamine agents and phenobarbitone [10, 18]. Characteristic biochemical abnormalities were elevations in the serum concentrations of bilirubin, alkaline phosphatase and γ glutamyl transferase. Variable, though lesser elevations in the aminotransferases have also occurred.

In the majority of cases (68%) the onset of symptoms occurred after cessation of flucloxacillin treatment (mean 16.6 days: range 1-42). The course of the illness was typically protracted, averaging some 11 weeks. Liver function tests remained abnormal after resolution of symptoms in 42% of cases, for an average of 5 more weeks. One report described severe cholestasis persisting for more than 7 years following an 18 day course of flucloxacillin [18].

Pathology and pathogenesis

The majority of reports has described a moderate to severe cholestatic hepatitis. Prominent features have included centrilobular bile stasis with canalicular dilatation, portal inflammatory cell infiltrate comprised predominantly of lymphocytes but sometimes with prominent eosinophils, and mild to moderate fatty infiltration. Of particular interest and importance are the reports of interlobular bile duct damage, with oedema, degenerate epithelium and disappearance of the ducts [10, 11]. Thus, flucloxacillin should be added to the list of drugs responsible for the “vanishing bile duct syndrome”, which is an established cause of protracted severe cholestasis [23, 24]. Fibrosis has been reported in one case [10] and cirrhosis in another [18].

In vitro immunological studies involving the lymphocyte transformation test [8] and the leukocyte migration inhibition test [4] have demonstrated findings consistent with sensitisation to the drug itself or to part of the molecule. These studies, together with the low incidence of the reaction and its unpredictability, are strongly in favour of an idiosyncratic, immunologically mediated, hypersensitivity reaction to the drug and/or to a metabolite. In the Australian data, there was no correlation between the severity of disease and the dose administered. Also noteworthy was the failure to demonstrate these in vitro immunological changes during prednisone therapy [7] as well as the fall in serum bilirubin and hepatic enzymes in some cases after corticosteroid therapy. However, there is no convincing evidence that such treatment alters the natural history of the reaction.

Risk factors and frequency of the reaction

These issues have been examined in three publications [18, 25, 26]. Risk factors were probably best defined by a combined retrospective/prospective case control study in Melbourne [25]. This involved 51 patients and 199 controls, consisting of individuals who took flucloxacillin but did not develop cholestasis. In the 51 cases, a combination of age exceeding 55 and duration of treatment exceeding 14 days yielded an odds ratio of 17.0 (95% confidence interval, 5-57.8: reference odds ratio of 1.0 for age 55 y or less and duration of treatment 14 days or less). The effect of age is also illustrated by the observation that, at the time of the study, only 16% of Australian prescriptions for flucloxacillin were for individuals aged 55 y or more, whereas this age group constituted 61% of the cases studied [25]. Derby et al [26] examined the frequency of the reaction in a cohort study of 132,087 individuals in the United Kingdom who had received flucloxacillin. They concluded that flucloxacillin was a likely cause of cholestatic hepatitis with an estimated risk of about 1 per 13,000 users. In an update of this study, involving a further 77,555 individuals who took flucloxacillin