6. ADVERSE REACTIONS AND TOXICITY

In general, fusidate sodium can be regarded as a nontoxic antibiotic. When administered orally, only mild upper gastrointestinal discomfort and diarrhea have been noted. Investigations have failed to show any evidence of renal or hemopoietic toxicity. There is a risk of thrombophlebitis after intravenous administration into a peripheral vein for more than 24 hours (Iwarson *et al.,* 1981), but this appears to be lower with the newer sodium fusidate intravenous formulation. No severe allergic reactions have been observed, but occasional mild rashes have been reported. The drug appears to be safe in penicillin-allergic patients. Allergic contact dermatitis has been reported after topical fusidate sodium use. In one case this was attributed to formaldehyde in the ointment (Andersen *et al.,* 1983). In chronic infections, fusidate sodium has been given for several months without obvious toxic effects (Crosbie, 1963; Dodson, 1963).

It is not known whether fusidate sodium accumulates in the presence of liver disease, and therefore it should be used cautiously in patients with impaired liver function. It seems safe in patients with cholestasis. Used intravenously, the drug does appear to impair liver function. In a group of patients with staphylococcal septicemia treated with intravenous fusidate sodium or other antibiotics, the rates of development of jaundice in these two groups were 34% and 2%, respectively. Of the jaundiced patients, 48% received the old fusidate sodium intravenously compared with 13% by mouth; jaundice appeared within 48 hours of commencing this drug in 93%; it was associated with deepening of jaundice in 68% of those with preexisting jaundice (Humble *et al.,* 1980). When fusidate sodium was stopped, serum bilirubin values fell to normal within 4 days in those who were anicteric before treatment. In 6 of 32 patients receiving the drug intravenously, liver function test results suggested a cholestatic picture; in the remainder, the mechanism of production of jaundice was unknown (Humble *et al.,* 1980; McAreavey and Redding, 1983). The new intravenous sodium fusidate preparation can also cause jaundice; whether it does so less frequently is not yet clear. Some 6% of patients receiving the new film-coated sodium fusidate tablets also have developed jaundice (Eykyn, 1990; Portier, 1990).

Because of the steroid structure of fusidate sodium, it was thought that this drug may possibly have some metabolic effects unrelated to its antibacterial activity. Wynn (1965) showed that no significant metabolic changes were associated with fusidate sodium administration. It had a mild protein catabolic effect, it lowered urinary calcium excretion, and it also caused mild temporary impairment of bromsulphthalein excretion by the liver. It is conceivable that the latter finding may have some relation to the ability of the drug to impair liver function. Human leukocytes incubated with fusidate sodium show markedly depressed migration (Forsgren and Schmeling, 1977). The clinical significance of this observation is unknown.

The drug is strongly bound to human albumin and competes with bilirubin for binding sites. It should therefore be administered with caution to newborn infants, particularly if premature, icteric, or acidotic, to avoid the risk of bilirubin encephalopathy induced by displacement of bilirubin from the carrier protein (Brodersen, 1985).

7. CLINICAL USES OF THE DRUG

Fusidate sodium is primarily used to treat staphylococcal infection. Although effective, it is not recommended for initial monotherapy of severe staphylococcal infections owing to its bacteriostatic activity and the high risk of development of resistance. Other drugs such as the penicillinase-resistant penicillins are preferred. Oral fusidate sodium may be useful for continuation oral therapy after the acute phase of the illness has responded, but it is mainly a reserve drug for the treatment of infections caused by methicillin-resistant strains. Resistant *S. aureus* strains emerge very easily *in vitro* and have appeared *in vivo* during the treatment of burns (Lowbury *et al.,* 1962), and during treatment of MRSA nasopharyngeal carriers (Chang *et al.,* 2000).

It is recommended that fusidate sodium be combined with another antistaphylococcal agent, particularly for treatment of infections caused by methicillin-resistant staphylococci (Jensen, 1968; Jensen and Lasen, 1969). Such combinations do not act synergistically, but may prevent the emergence of further drug resistance (Drugeon *et al.,* 1994). This applies to combinations of rifampicin–fusidate sodium and novobiocin–fusidate sodium (O'Neill *et al.,* 2001).

7a. Sepsis and endocarditis

Most clinical studies, all retrospective, show that the results of treatment of sepsis and endocarditis with sodium fusidate mostly in combination with other antibiotics have been good (Crosbie, 1963; Jensen and Lassen, 1964; Coombs and Menday, 1985). Fusidate sodium given intravenously has been used successfully to treat severe staphylococcal infections (Eykyn, 1990; Portier, 1990). Gosden *et al.* (1997) reviewed the outcome of more than 300 *S. aureus* bacteremia cases with focus on effect of fusidic acid, which was always given in combination with flucloxacillin (Gosden *et al.,* 1997). Factors predictive for survival were treatment with flucloxacillin, increasing duration of treatment, and presence of intravenous device or skin lesion. Prevention of relapse was associated with combination of flucloxacillin and fusidic acid (Gosden *et al.,* 1997). Antagonism between fusidate sodium and penicillin G (or one of the semisynthetic penicillins such as methicillin) can be readily demonstrated *in vitro* with many staphylococcal strains (O'Grady and Greenwood, 1973; Østergaard, 2003). Hudson (1985) reported a child with staphylococcal endocarditis who failed to improve after treatment with a combination of fusidate sodium and flucloxacillin, when reasonable bactericidal serum titers were achieved. Clinical improvement occurred only when fusidate sodium was ceased and flucloxacillin was continued alone. One animal study with induced MRSA endocarditis