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Editorial

Actinomycin D, Hepatic Toxicity and Wilms' Tumour—a Mystery Explained?

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ACTINOMYCIN D is a useful agent in the armamentarium of the paediatric oncologist, with special importance in the therapy of Wilms' tumours and soft tissue sarcoma [1, 2]. It is mainly used in combination with vincristine with or without an anthracycline or alkylating agent. In adult practice, it is used only in the treatment of Ewings' or peripheral neuroectodermal tumours and some malignant germ cell tumours. Actinomycin D was found to have activity against human tumours in the 1950s and in 1966 Farber [3] used it to treat children with Wilms' tumour [4]. Since then, the outlook for children with Wilms' tumour has improved dramatically. Now that most children are completely cured from the disease, one of the most important issues is 'the identification of the minimum necessary therapy' [1]. Currently, most children with Wilms' tumour are treated with vincristine and actinomycin D with or without abdominal or lung radiation and doxorubicin, according to the disease stage, the histological subtype and age of the child.

Actinomycin D is generally well tolerated, with alopecia, myelosuppression and vomiting as the main side-effects. Hepatotoxicity is also seen following actinomycin D but, rather oddly, almost exclusively in children treated for Wilms' tumour [5]. There are only anecdotal, sometimes unconvincing, accounts of this problem in children with soft tissue or bony sarcomas, despite identical dosages and scheduling. The incidence reported from different Wilms' tumour series varies from 1.7 to 13.5% [6–8]. The problem usually presents after the first 2 or 3 injections of actinomycin D, often suddenly and dramatically, with fever, anaemia, thrombocytopenia and a 'transaminitis'. In severe cases, jaundice and ascites may develop. The children are often quite unwell, requiring blood product and intensive care support and, although most make a full recovery, some fatalities have occurred. Hepatic veno-occlusive disease (H-VOD) has generally been considered as the likeliest cause of actinomycin D related 'hepatopathy', based on clinical and laboratory findings, but convincing histopathological data are scarce. Liver biopsies have rarely been performed during the course of the acute illness, because of thrombocytopenia and disordered coagulation. Raine and colleagues [6] described the experience of the United Kingdom Children's Cancer Study Group (UKCCSG) Wilms' tumour studies UKW1 and UKW2. As the exact pathogenesis was unknown, non-committal terms such as 'severe hepatic toxicity' or 'hepatopathy-thrombocytopenia syndrome' were used to describe the problem. Other authors have assumed the cause of the problem to be H-VOD. In the study of Bisogno and colleagues [7], describing the experience of the International Society of Paediatric Oncology (SIOP) group using the SIOP-9 protocol, 16 children underwent liver biopsies, but usually at the time of nephrectomy several weeks or months later, when liver function had improved. The findings were said to be consistent with H-VOD in nine instances. However, a central review of the slides was not apparently undertaken and no photomicrographs were provided. Currently, we feel that there is not enough evidence to assume that the pathogenesis is H-VOD, and in this publication we use the term 'actinomycin D-related hepatopathy'.

As the outcome for children with Wilms' tumour is now excellent, it is important to recognise and minimise treatment related toxicity. Therefore, the definition of risk factors for actinomycin D related hepatopathy is important. The first and most obvious risk factor is having a Wilms' tumour rather than another type of childhood cancer. In a review of the published literature, Kanwar and associates [5] identified a total of 49 cases of 'chemotherapy-associated VOD'. 45 of these patients had received actinomycin D and 41 had Wilms' tumour. The 4 children who had not received actinomycin D included 3 cases of children treated with daunorubicin, cytosine arabinoside and thioguanine (DAT) for acute myeloid leukaemia and 1 child with Wilms' tumour who had received vincristine only. Several other possible risk factors, including halothane (or similar) anaesthesia, vincristine therapy and pre-existing viral hepatitis have also been considered. None was considered likely to be a major risk factor [6, 8].

Neither does it seem likely that disease stage is especially important. Of the 41 cases reported by Bisogno and colleagues [7], 21 were stage I, 9 stage II and 11 stage III. In the Bisogno series, more children (19.6%) with stage 3 disease developed the complication, compared with those with stage

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I or II disease (both 7%). However, this may be because stage III patients also receive radiation therapy (see below). The influence of inferior vena caval involvement, which might impair hepatic venous flow, cannot be evaluated because of insufficient data.

Abdominal radiation, added to chemotherapy, probably increases the risk of hepatotoxicity and two of the earliest reports concerned children treated with combination chemotherapy, including actinomycin D and radiotherapy [9, 10]. Interestingly, each of these tumours was specifically reported to be in the right kidney, so the radiation dose to the liver was relatively high, as was the volume of irradiated liver. In the SIOP series [7], 11 (16%) of 68 children who had received abdominal irradiation developed hepatopathy, compared with 30 (6.7%) of 443 who had not been irradiated. Multivariate analysis confirmed the importance of radiotherapy as a risk factor ($P = 0.001$).

Consideration of the importance of actinomycin D dose and scheduling is hampered by variation in the regimens employed by the different national study groups who have reported chemotherapy related hepatopathy. In the National Wilms' Tumour Study 4 (NWTS 4) [8] actinomycin D was administered on a μg/kg basis. Patients were randomised to receive, every 3 weeks, either a single dose of 60 μg/kg (approximately 1.8 mg/m^2) and the same dose fractionated over 5 days. Of 37 children treated with the single dose schedule, 5 developed some degree of hepatic toxicity, between one and three doses. There was no measurable hepatopathy in the 63 children treated with the divided dose regimen. The possibility of a schedule-dependent effect was considered, but in a randomised Brazilian study, where identical doses and schedules were employed, the incidence of hepatotoxicity seen in both the single dose and fractionated dose arms was similar [11]. Because of the high incidence of liver toxicity in the early stages of NWTS 4, the dose of actinomycin D per course in NWTS 4 was reduced to 45 μg/kg. In the UKW1 and UKW2 studies, a pulsed 3 weekly actinomycin D dose of 1.5 mg/m^2 was consistently used [6]. 6 (1.7%) of a total of 355 children receiving vincristine and actinomycin D developed hepatopathy. In SIOP 9, a total of 511 eligible patients were randomised between 4 or 8 weeks of pre-operative vincristine and actinomycin D chemotherapy. The dose of actinomycin D was 0.45 mg/m^2 day for 3 days (later changed to 15 μg/kg day for 3 days) during weeks 1 and 2, repeated during weeks 4 and 5 in those randomised to the 8 week chemotherapy arm. Infants aged less than 1 year received 66% of these doses. 64 children suffered at least one episode of hepatotoxicity and 41 of 511 (8%) were classed as having 'H-VOD'. These variations in the reported incidence of hepatotoxicity are probably, at least in part, accounted for by dose and support the notion that there is a steep dose/toxicity relationship for hepatotoxicity between 1.5 and 1.8 mg/m^2 [12]. Kanwar and colleagues [5] reported one of the few convincing cases of hepatopathy following actinomycin D therapy for rhabdomyosarcoma in a 3.8 year old child who had received 2.25 mg/m^2 in divided doses, again suggesting that dose *per se* is important.

Young age and/or low body weight, have also been proposed as risk factors. Pochedly [13] reported the case of a newborn infant developing fatal hepatopathy after 75 μg of actinomycin D given daily for 5 days (the weight of the baby was not provided, but if one assumes a weight of 3 kg, the total dose in this case was very high—around 100 μg/kg). Pochedly also referred to 3 other cases of sudden death in infants with Wilms' tumour in the 1960s and suggested that actinomycin D should not be given to very young children. In the SIOP 9 study, infants received either 0.9 mg/m^2 or 30 μg/kg total dose per week, for 2 consecutive weeks. By univariate analysis the 'H-VOD' cases in SIOP 9 were both younger ($P = 0.008$) and weighed less ($P = 0.07$) than those without the complication. Because of concerns in the U.K. that infants were being relatively underdosed, recommendations in the current UKCCSG Wilms' study (UKW3) were changed from a dose based on body weight to a dose based on surface area. 5 of 9 infants on the new regimen developed hepatopathy, one episode of which was fatal. Whether this was a consequence of over-dosage, or because of genuine vulnerability of smaller and younger children is impossible to assess with these small numbers, but the UKCCSG has now reverted to dosing based on body weight. Infants may be more vulnerable to actinomycin D-related hepatopathy than older children, because of a lower toxicity threshold.

In this issue (pp. 1220–1223), Tournesello and colleagues provide convincing evidence for a strong association between Wilms' tumour arising in the *right* kidney and the development of actinomycin D related hepatopathy. In their study, children with right-sided Wilms' tumour developed a hepatopathy much more commonly than those with a left-side tumour (5.6% versus 1.2% $P = 0.0002$). They describe 2 cases of children with right-sided Wilms' tumours receiving vincristine plus actinomycin D chemotherapy according to the SIOP 9 study schedule who developed 'H-VOD' (they assumed that H-VOD is the cause of the syndrome). 1 child underwent a liver biopsy 3 weeks later, at the time of nephrectomy. They also reviewed the literature and documented the side of the tumour in those children who had developed 'H-VOD'. Of a total of 33 cases of 'H-VOD' reported in four series, 27 had a right-sided tumour. Tournesello and colleagues speculate that the association between right-sided Wilms' and actinomycin D related hepatopathy must be the consequence of hepatic congestion as a result of a 'mass effect', with partially obstructed hepatic venous return. In cases in which hepatopathy has developed, the tumours have often been referred to as 'large', but Wilms' tumours *are* 'large'! In UKW1, for instance, the median weight of stage I tumours was 525 g (range 50–2150 g) and that of stage II tumours was 750 g (range 90–2375 g) (data not shown, J. Imeson, U.K. Children's Cancer Study Group) The syndrome also occurred in 6 children with left-sided Wilms' tumours. Perhaps these particular tumours were large enough to compromise hepatic venous return from both lobes of the liver.

There are similarities, but also differences, between the clinical features of actinomycin D related hepatopathy and H-VOD following marrow ablative therapy and bone marrow transplant (BMT). The most typical clinical features of H-VOD following BMT are jaundice, painful hepatomegaly, ascites and unexplained weight gain [14]. Although the patients with post-BMT H-VOD may seem relatively well at first, the complication has a very high mortality, perhaps because of other factors such as graft-versus-host disease. In contrast, the onset of actinomycin D-related hepatopathy seems more acute and fever is common. A dramatic drop in the platelet count, rather than jaundice, is usually the first noted laboratory abnormality. Liver enzymes rise steeply, but the majority of patients survive, albeit with intensive support, including a period of ventilation whilst hepatic encephalopathy resolves.

Thus, children with right-sided Wilms' tumours of all stages, especially infants, are at increased risk of actinomycin D-related hepatopathy. Unexplained weight gain may also be a warning sign. Is the problem preventable? More cases occur after the second or third doses of the drug than the first (3 of 5 [8], 6 of 6 [6]). In the SIOP 9 series, the median time from diagnosis to the development of H-VOD was 55 days (range 8–147). Regular monitoring of liver function tests and full blood counts, weekly, after the first dose of actinomycin D, may detect some 'sub-clinical' cases, allowing omission or reduction of the next dose of actinomycin D. Careful attention to dosing is important, especially in young children. The high incidence of hepatic toxicity in SIOP 9 may well have been related to the fact that doses were given on a weekly basis. This schedule now seems inadvisable. A formal study of the ultrasonographic appearances of the liver, including Doppler studies of hepatic and portal venous flow, is now needed in children with Wilms' tumour during the first 8–10 weeks of actinomycin D-containing chemotherapy.

After an episode of hepatopathy, can actinomycin D be safely re-introduced? Probably, since recurrence of the problem seems uncommon. None of the 5 cases in the series reported by Raine and colleagues [6] had a second episode of hepatotoxicity after re-introduction of the drug. In the series reported by Bisogno and associates [7], 36 patients were given actinomycin D again with only one recurrence. Of the infants in UKW 3, which is as yet incomplete, just 1 child suffered a second episode after retreatment following tumour recurrence. It may, therefore, be safe to re-introduce actinomycin D after liver function and the platelet count have returned to normal.

Is survival or event-free survival compromised by these delays and/or dose reductions? In the SIOP 9 series, event-free and overall survival were the same in children who developed H-VOD as in those who did not, suggesting that, overall, these children did not suffer as a result of 'missed' or delayed doses. However, for higher stage tumours, there is an understandable reluctance to defer therapy for long, especially as there is no regimen with proven equal efficacy to vincristine, actinomycin D and doxorubicin. In these difficult cases, decisions must be made on an individual basis.

In conclusion, it seems likely that the most important factor contributing to the development of actinomycin D-related hepatopathy is the presence of a right-sided Wilms' tumour. Young age, low body mass and dose of actinomycin D are less important, but contributory factors. Obstruction to hepatic venous drainage, especially by right-sided tumours, probably predisposes to a form of H-VOD following actinomycin D therapy. Hepatic venous drainage is presumably most impaired early on in treatment because of the 'mass effect' of the tumour, explaining the almost exclusive occurrence of the syndrome during the first 10 weeks of chemotherapy. This particular oncological 'mystery' has probably now been solved by Professor Mastrangelo's group, not as a consequence of an expensive 'high-tech' research technique, but on a low budget by acute clinical observation and sheer diligence!

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