Eur J Cancer Clin Oncol, Vol. 21, No. 8, pp. 893-895, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Perspectives and Commentaries

How much does Liver Disease affect the Pharmacokinetics of Adriamycin?

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(A COMMENT ON: Ballet F, Barbare JC, Poupon A. Hepatic extraction of adriamycin in patients with hepatocellular carcinoma. *Eur J Cancer Clin Oncol* 1984, **20**, 761-764.)

ADRIAMYCIN is the most widely used representative of the anthracycline group of cytotoxic drugs, the reason being its broad range of activity in human tumours [1]. Twelve years ago pharmacokinetic studies indicated that adriamycin had a long biological half-life in man, and on this basis a single bolus dose regimen of 60 mg/m^2 every 3 weeks was recommended [2]. Recently, however, alternative schedules such as the use of a continuous infusion or a low-dose weekly schedule have been advocated. Although guidelines for these more recent schedules are not clear, it has been established that because of enhanced toxicity, dose modifications using the 3-week intermittent schedule are required in patients with severe hepatic dysfunction [3]. These recommendations were made 10 yr ago as the result of a study performed at the National Cancer Institute, U.S.A. which reported a clear relationship between toxicity, liver function abnormalities and disordered adriamycin pharmacokinetics in patients receiving intermittent bolus treatment.

Thus analysis of the pharmacokinetics of adriamycin may well be important in predicting the toxicity of treatment. In addition, it has been claimed that such analysis may be useful in predicting the response to treatment with adriamycin (for breast cancer [4] and for leukaemia [5]). Although these studies are open to some degree of criticism, the possible relationship between pharmacokinetics and response is clearly an area for further study.

Accepted 8 January 1985.

Following injection, adriamycin undergoes extensive metabolism, and two major pathways have been identified [6], although inter-patient variations probably exist and further investigation into the quantitative metabolism of adriamycin is required. In one study six different metabolites were separated using thin-layer chromatography from patient plasma following injection [7], and clearly interpretation of adriamycin metabolism will vary according to analytical techniques. However, the major route of biotransformation is probably reduction to the alcohol, adriamycinol, by a cytosolic NADPH-dependent reductase. It is of interest that adriamycinol itself possesses significant cytotoxic activity. The other route is a complex reduction of both adriamycin and adriamycinol to inactive 7-deoxyaglycones by microsomal reductases with the generation of free radicals. Although the liver is not the only organ in which metabolism of adriamycin occurs, it is probably the major site of biotransformation in man.

The major route of excretion for both adriamycin and metabolites is biliary, and in those patients in whom biliary excretion is severely impaired, i.e. those with hyperbilirubinaemia, delayed clearance of adriamycin and metabolites has been established [3]. It is also theoretically possible that other, more subtle abnormalities of liver function may affect the pharmacokinetics of adriamycin, and this aspect has been recently re-examined in the paper of Ballet *et al.* recently published in the *European Journal of Cancer & Clinical Oncology* (1984, **20**, 761-764).

Their study attempted to examine the ex-

traction of adriamycin from the liver by means of hepatic venous sampling, in five patients with hepatic cirrhosis and hepatocellular carcinoma. As the authors pointed out, the presence of cirrhosis may well affect the pharmacokinetics of drugs metabolised by the liver, and if this were true for adriamycin it might have important implications for its use, particularly in hepatocellular carcinoma arising in a cirrhotic liver, since adriamycin is one of the few drugs with proven (if only modest) activity in this tumour [8].

Using indocyanine green as a comparative measure of hepatic extraction, the authors reported a diminished hepatic extraction ratio for adriamycin with values of less than 0.10. They suggested that this indicated "an impairment of the cellular transport of adriamycin" within the liver. It should be noted that the liver function abnormalities reported in these patients were relatively modest.

The hepatic extraction ratio in this study was calculated as the plasma concentration of adriamycin in the femoral artery minus the concentration in the right hepatic vein divided by the concentration in the femoral artery. Although this method of calculation is standard, there are other methodological problems in this study.

Firstly, it is important in such studies to separate clearly measurement of adriamycin from that of the metabolites; this is particularly important since metabolite levels in samples from the hepatic vein are likely to be elevated in comparison to arterial levels. A clear distinction between adriamycin and metabolites is not clearly drawn in the description of the HPLC assay used by Ballet *et al.* A recent report from this laboratory highlights the importance of a precise HPLC technique, and indicates the possibility of confusing the native drug with its metabolites [9]. Clearly, if this occurred, calculations of hepatic extraction ratio of adriamycin (and adriamycinol) would not be valid.

Secondly, the time of sampling varied from 20 min to 6 hr following the injection of adriamycin. Since the release of adriamycin and its metabolites from the liver will vary with time, calculations of the hepatic extraction ratio using these data may be misleading. A more accurate estimate would generally be given when there is a steady level of drug, i.e. during a constant infusion, as described by Garnick *et al.* [10].

Thirdly, the metabolism and extraction of adriamycin by the liver may be profoundly affected by other drugs such as phenobarbitone (which causes enzyme induction) and cimetidine (which decreases liver blood flow). The documented interval of 48 hr during which other drugs were not given prior to study would be insufficient to allow for such effects to be dissipated in these patients.

The conclusion of Ballet *et al.* was that impairment of adriamycin hepatic extraction does exist in patients with hepatocellular carcinoma even in the absence of severe liver dysfunction. This conclusion is in contrast to that of Garnick *et al.* [10], who also examined the hepatic extraction of adriamycin in cancer patients with abnormal liver function (though not cirrhosis). They reported an extraction ratio for adriamycin of up to 0.5, calculated from simultaneous hepatic vein and hepatic arterial blood samples taken throughout a 4-hr adriamycin infusion. They also reported a negative extraction ratio for adriamycinol, reflecting the hepatic metabolism of this metabolite, which consequently reached higher levels in the hepatic vein than the artery.

The results of Ballet *et al.* are also in contrast to those of Chan *et al.* [11], who performed a similar study of the pharmacokinetics of adriamycin in hepatoma patients with cirrhosis, although in their study hepatic extraction was not specifically examined. However, it was shown that in seven hepatoma patients, all of whom had some liver dysfunction, adriamycin pharmacokinetics were not significantly different from those in normal patients. Clearly, if a major difference in hepatic extraction had occurred as suggested by the study of Ballet *et al.*, this should have been reflected in differences in pharmacokinetics. Chan *et al.*, however, did demonstrate a delay in the appearance in the serum of adriamycinol, as well as delayed clearance of this metabolite in the cirrhotic patients. Presumably this was the result of liver dysfunction, and although the clinical significance of this observation is unclear, it remains conceivable that the presence of hepatoma and/or cirrhosis does in fact have an effect on the metabolism of adriamycin. Preliminary studies in our laboratory have also documented similar variations in the clearance of metabolites in patients with hepatic dysfunction, and further studies specifically examining the pharmacokinetics of the major metabolite, adriamycinol, are clearly indicated.

Recently the NCI group have reported again on the relationship between hepatic dysfunction and the pharmacokinetics of adriamycin [12], and they have found no clear correlation between liver function tests, the presence of liver metastases and pharmacokinetic parameters including $t_{½}\ \alpha$ and $t_{½}\ \beta$. In this study patients were divided into those with a normal bromsulphalein (BSP) retention and those with elevated BSP retention as an index of liver dysfunction. Doses of adriamycin were the same in both groups and there was no difference

in toxicity or in response to treatment (for leukaemia). At first sight it would appear that these data conflict with the earlier data from Benjamin *et al.* [3] and also Lee *et al.* [13], who had also found that adriamycin clearance was delayed in patients with hepatic dysfunction, particularly hyperbilirubinaemia. It seems likely, however, that the explanation lies in the degree of liver dysfunction and that abnormalities of adriamycin pharmacokinetics are unlikely to be seen unless liver dysfunction is quite severely impaired.

In summary, it would be appropriate to quote the conclusion of Myers [14], who stated in a recent review that "a convincing quantitative relationship" between liver function abnormalities and impaired adriamycin clearance has not been established.

Nevertheless it would seem logical, from the clinical point of view, to follow the current recommendations of the NCI group [12]. They suggest adriamycin dose reductions for patients with multiple hepatic abnormalities or significant elevation of bilirubin. In answer to the question "how much does liver disease affect the pharmacokinetics of adriamycin?", current information would suggest that in terms of hepatic clearance the effect is rather less than that inferred by the study of Ballet *et al.* in their patients with hepatocellular carcinoma. However, there is a lack of information on the possible effect of liver disease on the metabolism and clearance of adriamycinol relative to other routes of metabolism, and since this metabolite possesses cytotoxic activity, this area certainly merits further study.

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