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## Review

# Pharmacokinetics of Anticancer Agents in Patients with Impaired Liver Function

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**This report reviews published information on the clinical pharmacokinetics of antitumour agents in patients with liver dysfunction, associated with primary liver disease or liver metastases. Information was available for anthracyclines and their related compounds, antimetabolites, cyclophosphamide, vinca alkaloids, taxanes and epipodophyllotoxins. Changes in the pharmacokinetic profile or metabolism in patients with mild or severe hepatobiliary dysfunction are described and the relationships between serum levels, parameters employed for measuring hepatic function and toxic or therapeutic effects are examined. Current knowledge of the pharmacokinetics of antineoplastic agents in liver disease is far from complete, mostly obtained in small numbers of non-homogeneous patients often presenting only moderate liver dysfunction, and empirical guidelines for dose assessment are still largely applied in clinical practice. Because of the complex pathophysiological mechanisms of liver insufficiency in cancer patients, there is still doubt whether endogenous markers are useful. Although caution in treating cancer patients with liver insufficiency is compulsory, for most compounds there seems no need to recommend dose reductions for moderate impairment. However, for the tubulin acting agents, vincristine, vinblastine and possibly for paclitaxel and docetaxel, there is strong evidence that dose adjustment is mandatory in order to avoid excessive neutropenia and neurotoxicity.**


**Key words: antitumour agents, clinical pharmacokinetics, liver dysfunction, dose adjustment**
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## INTRODUCTION

LIVER DISEASE may have a substantial and unpredictable effect on drug kinetics by: (1) altering the intrinsic hepatic clearance; (2) reducing the metabolic capacity of the liver; (3) affecting excretion into the bile; (4) reducing the production of albumin thus decreasing serum, protein binding and increasing the fraction of free compound; and (5) affecting absorption from the gastrointestinal tract in cases of severe portal hypertension. Reduced hepatic clearance may be due to reduced hepatocellular uptake and, if concomitant portal hypertension and porto-systemic shunts are present, to reduced liver blood flow.

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In cancer patients, liver dysfunction may result from other diseases affecting the liver such as hepatitis or cirrhosis, from toxicity induced by chemotherapy or from deterioration of liver function in the presence of a neoplastic process which reduces the functioning, metabolising liver mass. Impaired drug clearance may be due to a decreased liver cell mass, to a reduced metabolising capacity of the hepatocyte or finally to a reduction of hepatic blood flow due to metastases compressing liver tissue.

Liver dysfunction may be important because of changes in the metabolism of anticancer drugs which undergo hepatic biotransformation, either producing active metabolites (e.g. cyclophosphamide, dacarbazine) or resulting in detoxified products (e.g. doxorubicin, mitoxantrone, vinca alkaloids. For drugs which are highly protein-bound (e.g. etoposide or anthracycline antibiotics), a condition of hypoalbuminemia,

which may result from severely impaired liver function, together with concomitant hyperbilirubinemia, which may be due to both severe liver impairment and severe cholestasis, may increase the fraction of unbound drug responsible for therapeutic and toxic effects [1–3].

Increased toxicity, sometimes associated with delayed drug clearance, has been described for a series of anticancer agents [4, 5] in patients with several biochemical indicators of liver dysfunction. To avoid toxicity, drastic dose reductions have often been suggested, but underdosage risks reducing the efficacy of the drug. There is a lack of reliable dosage modification schemes, based on detailed pharmacological studies in patients with liver disease.

Patient population studies are not homogeneous and often no detailed diagnosis is reported. In addition, information on the ultrasonographic and endoscopic signs of portal hypertension and on liver histology is only rarely reported. Therefore, the clinical data considered so far for their relationship with pharmacokinetic parameters are limited to biochemical indices, which unfortunately reflect a wide variety of pathophysiological changes.

This paper reviews the literature on the clinical pharmacokinetics of the most widely used antitumour agents, such as anthracycline antibiotics and analogues, alkylating agents, antimetabolites, epipodophyllotoxins, vinca alkaloids and taxanes, for which the question of dosage adjustment has been raised when a tumour involves the liver, or liver function tests are altered. Since in most studies the patients had mild or moderate liver dysfunction, resulting in only slight changes of the biochemical tests, it was not possible to relate modification of the pharmacokinetic profile with the degree of liver dysfunction.

Published studies were identified through a computer search for the period 1973–1996 using the Medline database of the National Library of Medicine (Bethesda, Maryland, U.S.A.) and by inspecting the bibliographies of original and review articles on the pharmacology of antitumour agents in patients with abnormal liver function.

## LIVER FUNCTION TESTS

The most commonly used liver function tests were serum biochemical indices. These tests, listed in Table 1, reflect a variety of pathophysiological changes of different degrees. For example, serum transaminases, ALT (alanine amino transferase) or SGPT (serum glutamic pyruvic transaminase), and AST (aspartate amino transferase) or SGOT (serum glutamic oxaloacetic transaminase) mainly reflect the degree of liver inflammation and are consequently related to hepatocellular necrosis. Therefore, it is not correct to employ AST and ALT as indices of liver function, and in any case no quantitative relationship can be established between liver function impairment and changes in serum transaminases. Serum bilirubin levels are mostly related to severe cholestasis or severe liver impairment. However, this parameter lacks sensitivity, since serum bilirubin only rises if there is very severe impairment [6]. The test also lacks specificity since it is also elevated in haematological conditions and in subjects with congenitally deficient hepatic conjugation [6]. This condition, known as Gilbert's syndrome, is highly prevalent in the general population, so it is questionable whether a mild increase of total bilirubin truly reflects impairment of liver function. Cholestasis may markedly affect the pharmacokinetics of drugs which are significantly excreted in the bile, and impaired liver function is also associated with reduced hepatic uptake and metabolism.

Reduced production of albumin, increased prothrombin time or serum pseudocholinesterase levels are other parameters widely used to measure liver function roughly. However, these were used very seldom in the papers reviewed.

Dynamic liver function tests such as antipyrine test, galactose elimination capacity, bromosulphthalein clearance and, recently, the mono-ethylglycine–xylidide test based on lidocaine metabolite formation [7, 8], would be more appropriate to evaluate quantitatively liver function. However, they are not widely used in clinical practice, because they are laborious, and were evaluated in only a few of the studies reviewed.

*Table* 1. *Pathophysiological significance of altered biochemical indices associated with liver dysfunction and their utility in assessing and quantifying liver impairment*

| Biochemical indices | Normal serum levels | Underlying pathophysiological condition | Limitations for clinical use | Relationship with impairment of liver function |
|---|---|---|---|---|
| Bilirubin | $\leq$ 1.2 mg/100 ml | Severe cholestasis<br>Impaired liver function | Low sensitivity<br>Low specificity | †Moderate: 2–3 mg/100 ml<br>†Severe: > 3 mg/100 ml |
| Transaminase:<br>Alanine amino transferase (ALT)<br>Aspartate amino transferase (AST) | *< 45 U.I./l | Inflammation<br>Cytolysis | Unrelated to liver function | No quantitative relationship |
| Alkaline phosphatase (APH) | *< 279 U.I./l | Cholestasis | Unrelated to liver function | No quantitative relationship |
| $\gamma$-glutamyl transferase ($\gamma$-GT) | *< 32 U.I./l in ♀<br>*< 50 U.I./l in ♂ | Cholestasis | Unrelated to liver function | No quantitative relationship |
| Pseudocholinesterase (CHE) | > 4600 U.I./l | Impaired liver function | Rough measure of liver function<br>Wide range of normality | Not well established |
| Albumin | > 3.5 g/100 ml | Impaired liver function | Rough measure of liver function<br>Influenced by nutrition | †Moderate: 3–3.5 g/100 ml<br>†Severe: < 3.0 g/100 ml |
| Prothrombin activity | 80–100% | Impaired liver function | Rough measure of liver function<br>Influenced by cholestasis | †Moderate: 40–70%<br>†Severe: < 40% |

*Most widely used range. †Moderate and severe impairment of liver function were defined on the basis of the widely used Child–Pugh classification of liver cirrhosis [93]. ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase).

## DOXORUBICIN

For doxorubicin (DOX) and all the anthracyclines that are primarily metabolised and excreted by the liver (Figure 1), pharmacokinetic alterations should be expected to be related to abnormal liver function, as in experimental animals [9]. The drug that has been most widely investigated in this regard is DOX and Table 2 summarises the main reports describing its pharmacokinetic behaviour in cancer patients with hepatic impairment.

The conventional guideline for clinical practice is mostly based on the early reports by Benjamin and associates [10, 11] describing elimination of DOX in the presence of liver disease, evaluated on the basis of serum bilirubin levels. However, these papers, which raised the question of liver function impairment in cancer therapy, suffer from many limitations, since they give few details on the pharmacology studies and make no mention of other liver function tests. The studies reported deal with 8 patients with abnormal bilirubin levels. 3 had serum bilirubin higher than 3 mg/100 ml, with severe pancytopenia and painful mucositis, and 3 drug-related deaths were observed. As plasma levels of DOX and its metabolites were very high in these patients, Benjamin suggested reducing the DOX dose by 50% for patients with serum bilirubin between 2 and 3 mg/100 ml or serum transaminases more than three times normal, by 75% for patients with serum bilirubin >3 mg/100 ml, and withholding treatment in patients with bilirubin > 5 mg/100 ml.

Administration of DOX to patients with hepatocellular carcinoma or with liver metastases, with mildly altered transaminase levels but normal bilirubin, results in some delay in elimination [12], reduced clearance and impaired hepatic extraction of the drug [13]. Preiss and associates [14] reported that the elimination rate of DOX correlated with that for antipyrine, which is a marker of liver monooxygenase metabolising capacity, despite the different elimination mechanisms of the two drugs.

Pharmacokinetic studies by other authors [15–18], using full or reduced DOX doses (15–45 mg/sq.m. i.v.) according to the scheme proposed by Benjamin, did not confirm the need for severe dose reduction of DOX in patients with moderate hepatic dysfunction. During treatment with reduced doses of DOX, patients with hepatoma and proven

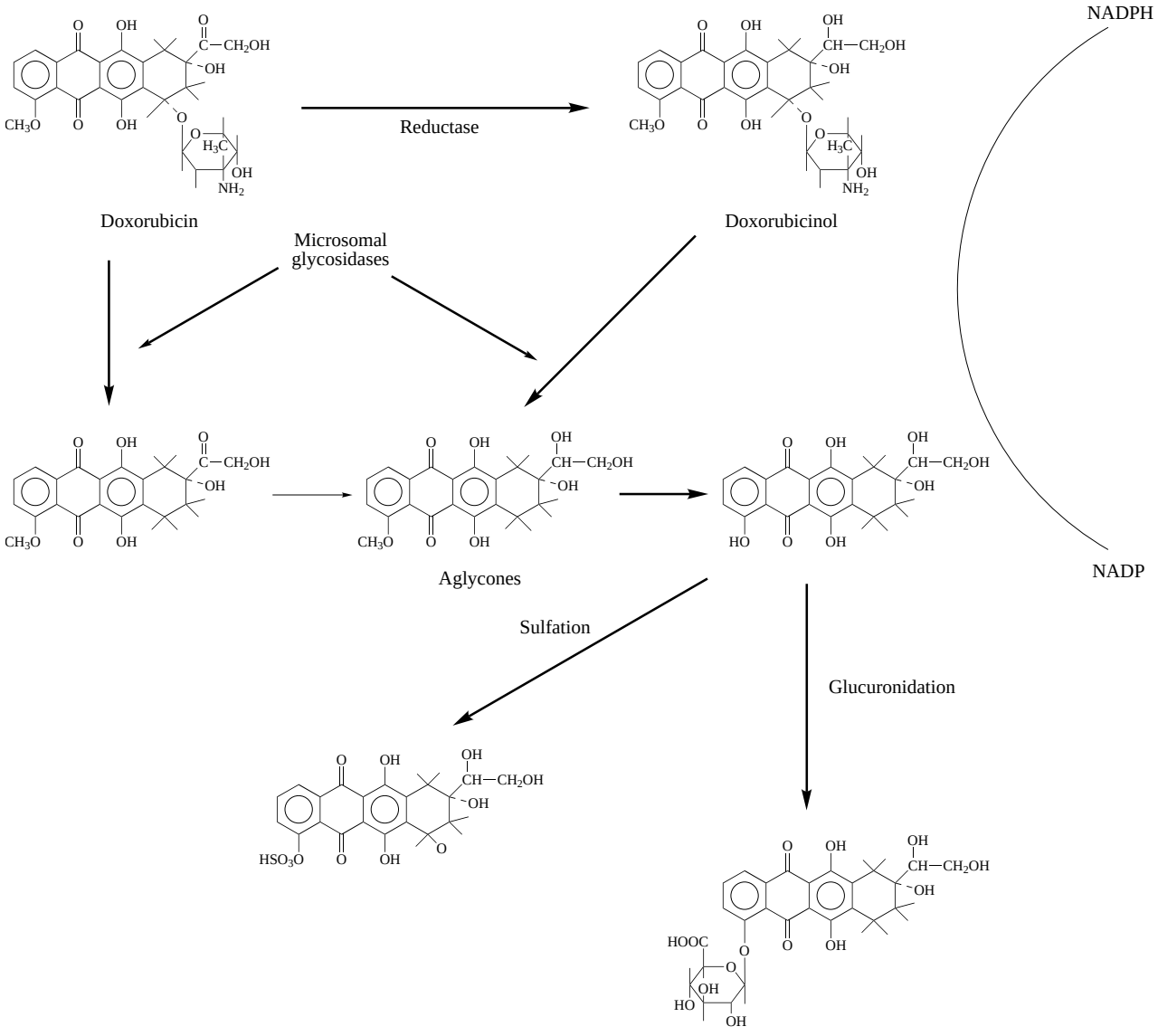


**Figure 1. Metabolic pathway of doxorubicin proposed by Bachur [94].**

*Table 2. Pharmacokinetics of doxorubicin (DOX) in cancer patients with liver dysfunction*

| Year | Study [Ref.] | Dose mg/sq.m i.v. | Diagnosis No. with liver dysfunction/total | Indices of liver dysfunction (mean value or range) | Pharmacokinetic behaviour in the presence of liver dysfunction and authors' comments |
|---|---|---|---|---|---|
| 1974 | Benjamin [10, 11] | 60 | Disseminated sarcoma (5/8) | Bil > 3 mg/100 ml | Plasma levels of DOX and DOXol 4–5 times higher, delayed drug elimination with severe pancytopenia. 75% dose reduction suggested for bilirubin > 3 mg/100 ml |
| 1980 | Chan [15] | 15–45 | Hepatoma or liver metastases (8/17) | Bil (3–10 × normal, 4 pts)<br>AST (8 × normal)<br>ALT (8 × normal) | Plasma profile of DOX normal, but delayed appearance and prolonged half-life of DOXol in patients with high bilirubin, treated with 1/3 of the dose |
| 1988 | Mross [12] | 40–56 | Breast cancer with liver metastases (3/8) | $\gamma$-GT (> 2 × normal)<br>AST (2–3 × normal)<br>ALT (2–3 × normal) | Delayed DOX elimination, but not clearly related to the degree of liver damage. Reduction of the dose for elevated transaminases does not alter pharmacokinetics as compared to normal patients |
| 1989 | Morris [17] | 12–44 | Extrahepatic tumours (5/15) | APH (mild increase)<br>$\gamma$-GT (mild increase) | Plasma profile apparently normal |
| 1992 | Johnson [19] | 60 | Hepatocellular cancer (16/30) | Bil (2 × normal)<br>AST (2–10 × normal) | AUC for DOX and DOXol increased and directly related to mild alterations of serum bilirubin. Neutropenia, although related to serum bilirubin, does not justify dose adjustment |
| 1992 | Piscitelli [18] | 45–72 | Small cell lung caner (4/31) | Bil (2–6 × normal)<br>$\gamma$-GT (> 10 × normal)<br>APH (> 4 × normal)<br>AST (> 5 × normal) | At 2-fold bilirubin no change in DOX profile, but at 6-fold bilirubin AUC was 3 times higher and terminal half-life significantly prolonged. Marked myelotoxicity associated with liver dysfunction |

For abbreviations see Table 1.
Bil, bilirubin; pts, patients; AUC, area under the concentration versus time curve.

cirrhosis or with liver metastases and slight elevation of transaminases and bilirubin had an apparently normal DOX profile. However, formation of the metabolite doxorubicinol (DOXol) was mostly slowed overall in patients with elevated bilirubin, and its half-life was prolonged with an increase in the ratio of DOXol to DOX area under the concentration versus time curve (AUC). These studies did not mention toxicity and therapeutic outcome in relation to pharmacokinetics. The observation by Brenner and associates [16] in acute myelocytic leukaemia (AML) may be noteworthy, although not applicable to solid tumours, as dose-limiting myelotoxicity due to chemotherapy is not a concern in AML. These authors reported that, whereas mildly abnormal liver function tests do not affect DOX clearance and toxicity, overt liver impairment, suggesting a conventional dose reduction, results in lower drug toxicity but also a shorter duration of response and survival. More recent studies [18, 19] show that the myelotoxicity of DOX at conventional doses (45–72 mg/sq.m.) is indeed affected by hepatic dysfunction as measured by serum bilirubin. In patients with hepatocellular carcinoma [19], the degree of toxicity was directly related to serum bilirubin concentration but not to any other liver function test or any pharmacokinetic parameter studied, including AUC or elimination half-life of DOX and DOXol. High bilirubin levels were associated with a higher AUC of the compound and more severe myelosuppression, but there was no evidence of a better response after a full dose of DOX in hyperbilirubinemic patients. In patients with small cell lung cancer, Piscitelli and associates [18] found a clear relationship between systemic exposure to DOX and DOXol, defined by AUC, and degree of myelosuppression. Patients with high bilirubin ($3.7 \pm 3.6$ mg/100 ml) and clearly abnormal liver function had lower DOX clearance and experienced marked myelotoxicity. These results suggest that, in agreement with previous reports for DOX and other anthracyclines [20–24], there is a significant pharmacodynamic relationship between systemic exposure (AUC) to DOX and myelosuppression. Other DOX-induced toxicities appear to be related to the peak plasma concentration rather than to AUC [25–27], and therefore prolonged infusion schedules have been attempted in order to lower the toxic peak concentrations while maintaining total drug availability [28].

Considering the whole pharmacokinetic literature and the conflicting reports, an indiscriminate dose reduction does not appear to be justified and may significantly reduce not only toxicity but also the therapeutic outcome. Only for severe liver impairment (i.e. in patients with serum bilirubin > 3 mg/100 ml), is dose adjustment advisable. The AUC of DOX at the first course of therapy may be estimated so as to tailor subsequent doses to each patient, and limited sampling strategies [29] may help to improve drug monitoring.

## ANTHRACYCLINE ANALOGUES AND RELATED COMPOUNDS

As far as anthracycline analogues are concerned (Table 3), the association between pharmacokinetics and liver disease has been widely investigated [30–34] for 4'epidoxorubicin (4'epiDOX). In patients with abnormal liver function tests or liver metastases, decreased clearance of 4'epiDOX with delayed plasma elimination of the native compound and of its reduced metabolite, 4'epidoxorubicinol, and increased AUC values of 4'epiDOX, have been reported by the majority of authors. As for DOX, conventional dose reduction of 4'epiDOX based on bilirubin levels has been suggested for clinical practice. These papers, however, give little reliable information about the clinical outcome of treatment. In patients with breast cancer, Speth and associates [31] and Jakobsen and associates [33] described prolonged half-life and reduced clearance of 4'epiDOX in patients with severe hyperbilirubinemia, as compared with patients with normal liver function.

Based on the finding of a reverse relationship between 4'epiDOX clearance and AST, Twelves and associates [34] suggested that serum AST, rather than serum bilirubin, might be the best indicator of liver impairment and may provide a more rational basis for dose reduction. A rise in AST, reflecting necrosis related to liver involvement by metastases, should arise earlier and precede alterations in bilirubin, which is a less sensitive parameter and reflects serious liver injury. Liver metastases result in an elevated AUC and reduced plasma clearance of 4'epiDOX with increased toxicity [30–35], thus suggesting the need for dose reduction.

In patients with liver dysfunction, 4'epiDOX glucuronidation is affected and the drug total body clearance decreases. Robert and associates [32] observed that patients with reduced hepatic synthesis of several proteins (fibrinogen and globulins) had limited liver glucuronidation capacity with low levels of inactive 4'epiDOX glucuronides and higher availability of the parent compound. These patients had a much lower percentage of change in granulocytes after therapy and responded better to treatment. In this connection the only 2 patients of Speth's group who achieved partial response had high bilirubin levels with increased concentrations of 4'epiDOX in blood and in haematopoietic cells.

Although the present studies do not permit any firm conclusion on the relationship between impaired liver function, 4'epiDOX pharmacokinetics and pharmacodynamic response, the observations reported do not indicate the need for dose reduction in the presence of mild liver dysfunction, but suggest caution in patients with liver metastases [34]. As observed for DOX by Brenner and associates [16] and by Speth and associates for this DOX analogue [31], higher drug levels may even result in a better response, although at the risk of heavier toxicity.

The pharmacokinetics of the daunomycin analogue, 4-demethoxy daunomycin (idarubicin), have been described by Zanette and associates [36] and by Camaggi and associates [37] in patients with different tumours and liver metastases, but normal or slightly altered bilirubin levels. Besides a somewhat lower plasma availability of the metabolite, i.e. reduced plasma AUC, no substantial difference was observed compared with patients without liver involvement. Unlike with 4'epiDOX, the pharmacokinetics of idarubicin was not significantly dependent on the presence of liver metastases, but was to some extent related to renal function, since a relationship was found between the clearance of the compound and creatinine [37].

Previous studies reported similar observations in 2 patients with gastrointestinal carcinoma and extrahepatic biliary obstruction [38] and in patients with different tumours and mild liver impairment [36]. However, although mild liver disease does not seem to require dose modifications, there is too little detailed information on the pharmacokinetic–pharmacodynamic profile in the presence of severe liver dysfunction to establish clear dosing guidelines for 4'epi-

*Table* 3. *Pharmacokinetics of anthracycline analogues and derivatives in cancer patients with liver dysfunction*

| Year | Study [Ref.] | Drug and dose mg/sq.m i.v. | Diagnosis No. with liver dysfunction/total | Indices of liver dysfunction | Pharmacokinetic behaviour in the presence of liver dysfunction and authors' comments |
|---|---|---|---|---|---|
| 1992 | Camaggi [30] | 4-epiDOX (50–90) | Solid tumours with liver metastases (6/17) | Bil, AST, ALT, APH (actual values not reported) | Decreased clearance of epiDOX in 2 patients, but unchanged pharmacokinetics of epiDOXol. Dose modification suggested in the presence of liver dysfunction |
| 1986 | Speth [31] | 4-epiDOX (20) | Breast cancer (2/12) | Bil (2–10 × normal) | Decreased clearance and prolonged half-life of epi-DOX and epi-DOXol, resulting in higher drug levels in white blood cells and improved partial drug response |
| 1991 | Jakobsen [33] | 4-epiDOX (63) | Breast cancer with liver metastases (3/78) | Bil (3–5 × normal) | Extremely long half-life and increased AUC |
| 1992 | Twelves [34] | 4-epiDOX (25) | Breast cancer (30/52) | Bil (2–10 × normal)<br>AST (2–5 × normal) | Epi-DOX clearance significantly reduced in patients with raised AST. Strong correlation between epiDOX clearance and AST, but not with bilirubin. Serum AST, rather than bilirubin, may be a better indicator for dose adjustment |
| 1990 | Zanette [36] | 4-DMDR (5) and 5, 10, 25 oral | Different tumours (7/28) | Bil (1.5–2 × normal, 3 pts)<br>$\gamma$-GT (2–8 × normal)<br>APH (1.5–6 × normal) | No changes in the kinetics of the drug and its metabolite, 4-DMDRol, in the presence of mild liver insufficiency |
| 1992 | Camaggi [37] | 4-DMDR (12) and 5, 10, 25 oral | Advanced cancer with liver metastases or liver dysfunction (11/21) | AST (1.5–4 × normal)<br>ALT (1.5–8 × normal)<br>APH (1.5–2 × normal) | Kinetics of the drug not significantly influenced |
| 1982 | Savaraj [39] | Mitoxantrone (1–12) | Epidermoid cancer of lung and colon (2/11) | Bil (> 2 × normal)<br>AST, APH (actual values not reported) | Decreased clearance and prolonged half-life. Dose modification suggested in liver dysfunction |
| 1986 | Smyth [40] | Mitoxantrone (14) | Extrahepatic tumours (2/11 with liver metastases) | Bil (> 2 × normal) $\gamma$-GT, APH (actual values not reported) | Prolonged half-life. Dose modification suggested in liver dysfunction |

For abbreviations see Tables 1 and 2.
4-DMDR, 4-demethoxydaunorubicin, 4-DMDRol, 4-demethoxydaunorubicinol.

DOX.

Controversial findings have been reported on the pharmacokinetics of the anthracenedione derivative, mitoxantrone. This compound, which is metabolised and eliminated primarily by the hepatic route, was described by Savaraj and associates [39] and by Smyth and associates [40] as being cleared more slowly, with a prolonged half-life, although not to a remarkable extent, in few cancer patients with apparently moderately abnormal liver function (only bilirubin was reported) or with hepatic metastases. Van Belle and associates [41] found no change in drug kinetics in 6 patients with liver metastases, even in one with jaundice, but no quantitative data on liver function were provided.

Overall, these findings, together with the observation that no unexpected toxicity was observed in these patients, suggest that dose adjustment is not indispensable in the case of modest liver dysfunction.

## ANTIMETABOLITES

Table 4 summarises the main studies on 5-fluorouracil, methotrexate and cyclophosphamide. Hepatic metabolism is the major route of elimination of 5-fluorouracil (5-FU). Christophidis and associates [42] studied 5-FU distribution in 12 patients with colorectal cancer, divided into two groups, with low or high drug availability, but differences in drug bioavailability were not related to differences in liver function or metastatic tumour deposits in the liver. Subsequent studies [43–46] of plasma and tissue concentrations of 5-FU or its derivatives in patients with hepatocellular carcinoma and liver cirrhosis or liver metastases detected no change in drug disposition in relation to liver dysfunction. It would thus seem that no dose adjustment is required for 5-FU and derivatives in this population.

In agreement with an old report [47] of altered drug clearance in patients with hepatic metastases, Port and associates [48] noted a different catabolism of 5-FU in the hepatic tumour tissue in patients with liver metastases from different primary tumours. This finding is difficult to interpret and has limited value on account of the very small number of patients involved.

For methotrexate (MTX) which is mainly excreted through the renal route and whose liver metabolite 7-hydroxy-methotrexate is quantitatively irrelevant, hepatic function is not expected to be involved in systemic clearance of the drug. Crom and associates [49] found that abnormal ALT concentrations were associated with lower drug clearance only in patients whose creatinine clearance was near the low limit of the normal range and, therefore, the liver may play an important role in systemic clearance only for these patients.

The impact of variability in MTX clearance on clinical outcome was clearly documented in children [50, 51]. Skoglund and associates [52] found no correlation between drug levels in plasma or urine and liver function tests in children with acute lymphocytic leukaemia and mild liver injury (no liver function test results are given) treated with oral MTX.

## CYCLOPHOSPHAMIDE AND RELATED COMPOUNDS

The pharmacokinetic profile of cyclophosphamide (CTX) in patients with liver dysfunction was investigated several years ago by Bagley and associates [53] who reported a prolonged half-life in one patient with cirrhosis and jaundice. Subsequent studies [54, 55] in patients with impaired liver function due to metastatic deposits in the liver [54] or to liver cirrhosis due to chronic hepatitis [55] are summarised in Table 4.

Systemic clearance of this compound, which undergoes extensive biotransformation to the active metabolite 4-hydroxy-CTX and then to the inactive 4-keto-CTX and 4-carboxy-CTX in the liver ([56] and Figure 2) should be influenced by liver function. However, in patients with moderate liver dysfunction, indicated by changes in pseudocholinesterase serum levels, reduced clearance and prolonged half-life of CTX, and the delayed appearance and inactivation of 4-hydroxy-CTX, overall exposure to the active metabolites does not change. In agreement with this pharmacokinetic finding, Juma [55] observed no clinical evidence of increased

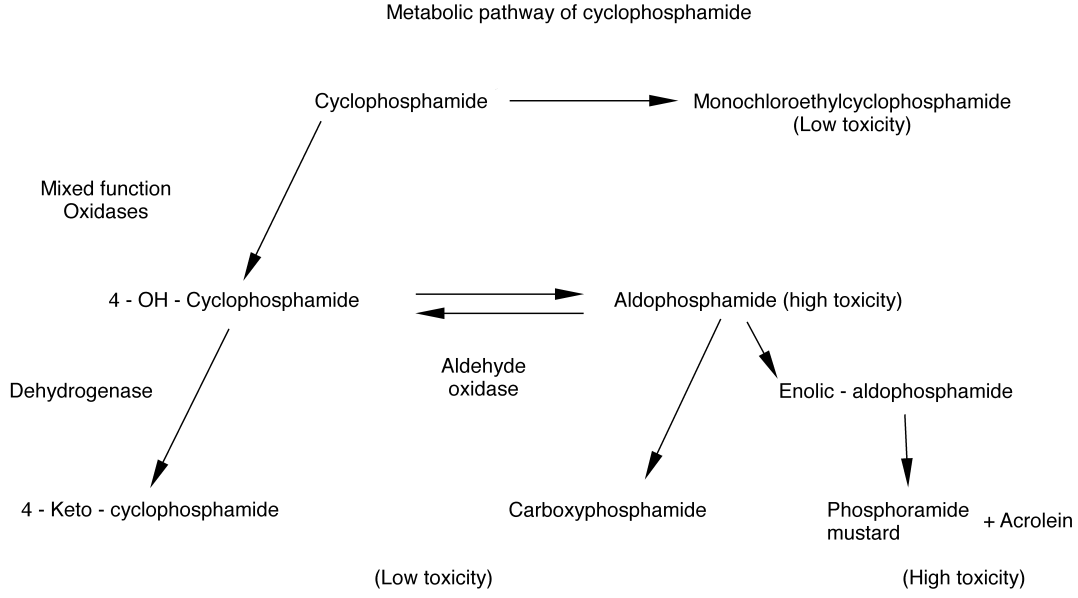


**Figure 2. Metabolic pathway of cyclophosphamide modified; by permission of *Biochemical Pharmacology* [95].**

*Table* 4. *Pharmacokinetics of 5-fluorouracil (5-FU), methotrexate (MTX) and cyclophosphamide (CTX) in cancer patients with liver dysfunction*

| Year | Study [Ref.] | Drug and dose mg/sq.m | Diagnosis No. with liver dysfunction/total | Indices of liver dysfunction | Pharmacokinetic behaviour in the presence of liver dysfunction and authors' comments |
|---|---|---|---|---|---|
| 1992 | Fleming [46] | 5-FU (552–1069 i.v.) | Head and neck cancer (187 patients, with and without liver dysfunction) | Bil, AST, ALT, APH, $\gamma$-GT (actual values not reported) | A poor linear correlation ($P < 0.05$) between drug clearance and liver dysfunction values was found only for APH, but not for the other liver tests. No dose reduction is indicated |
| 1994 | Skoglund [52] | MTX (4–29 per os) | ALL and non-Hodgkin's lymphoma (15/17) | Bil, AST, ALT, APH, $\gamma$-GT (mild alterations, but actual values not reported) | No correlation was found between serum levels of MTX or its 7-OH metabolite and liver function tests |
| 1980 | Von Wagner [54] | CTX (10 i.v.) | Metastatic carcinoma (10/20 with liver metastases) | CHE (< 3000 U/l) | Reduced clearance of native drug and lower serum levels of activated CTX. However, due to low renal clearance, AUC of CTX metabolites remains relatively unchanged |
| 1984 | Juma [55] | CTX (15 i.v.) | Hodgkin disease (7/17 with liver cirrhosis) | Bil (7 × normal)<br>AST (9 × normal)<br>ALT (6 × normal)<br>APH (8 × normal) | These patients with severe liver injury have a longer half-life and lower total body clearance of the native compound. No evidence of increased toxicity |

For abbreviations see Tables 1 and 2.
ALL, acute lymphocytic leukaemia.

*Table* 5. *Pharmacokinetics of vincristine in cancer patients with liver dysfunction*

| Year | Study [Ref.] | Dose mg/sq.m i.v. | Diagnosis No. with liver dysfunction/total | Indices of liver dysfunction | Pharmacokinetic behaviour in the presence of liver dysfunction and authors' comments |
|---|---|---|---|---|---|
| 1992 | Van den Berg [60] | 0.4–1.5 | Different tumours (15/39) | Bil (3 pts), AST, ALT, APH, $\gamma$-GT (actual values not reported) | Prolonged β half-life and higher plasma AUC account for reduced clearance in the presence of cholestasis |
| 1992 | Desai [61] | 1.4–2 | Leukaemia and lymphoma (11/27) | APH (83% increase in 5 pts) | Significant correlation between dose, AUC and neuropathy. Higher plasma AUC accounts for impaired drug elimination. Increased toxicity in patients with high APH suggests dose reduction, even with normal bilirubin and transaminases |

For abbreviations see Tables 1 and 2. ALL, Acute lymphocytic leukaemia.

toxicity even in patients with severely affected liver function, so apparently no dosage adjustment is needed in the presence of liver disease.

It is reasonable to assume that the same conclusions should apply to the CTX derivative, iphosphamide, which undergoes the same metabolic transformation, but whose pharmacokinetics in the presence of liver impairment has, to our knowledge, not been described.

## VINCA ALKALOIDS AND TAXANES

The tubulin acting agents are the only clear example (Table 5) of antitumour agents requiring dose adjustment in cancer patients with liver dysfunction: vincristine, vinblastine, apparently vinorelbine and the taxane compounds, paclitaxel and docetaxel.

A consistent finding in clinical trials after repeated doses of vincristine (VCR) is neurotoxicity, which is related to the cumulative dose [57]. As the biliary system is the main route of excretion of VCR and its desacetyl-metabolic products [58], it is reasonable to expect that, in spite of significant individual differences in the pharmacokinetics of VCR [59], hepatic dysfunction and especially cholestasis might alter elimination kinetics and increase exposure to the drug and its metabolites, thus increasing toxicity.

Van den Berg and associates [60] and Desai and associates [61] investigated the pharmacokinetic behaviour of VCR in patients with different tumours and cholestasis, with increased serum levels of alkaline phosphatase and, in several cases, also bilirubin. In patients with liver dysfunction, the half-life of VCR is more than doubled and the total availability, expressed by the AUC, is three times higher than in patients with normal liver function. Neurotoxicity was related to the dose and to the plasma AUC of the drug. Desai and associates [61] noted that in cholestatic patients, a small reduction in the drug dose resulted in lower VCR plasma AUC and less neurotoxicity. They did not indicate the extent to which alkaline phosphatase (APH) or bilirubin was raised in these patients. However, in view of the clinical evidence of toxicity, it is reasonable to recommend dose adjustment in the presence of cholestasis.

Similar considerations apply to the VCR related compound, vinblastine (VBL). Although a decrease in drug clearance seems related to the response rate [62], in patients who have received prolonged drug infusions high serum drug concentrations are only weakly associated with the severe leucopenia resulting from treatment, but strongly related to non-haematological toxicity [63]. These observations suggest that a dose reduction should also be considered in patients with liver dysfunction receiving this drug.

The new semisynthetic vinca alkaloid, vinorelbine, has been investigated in advanced breast cancer patients with liver metastases [64]. In patients with severe liver dysfunction, indicated by the dynamic mono-ethylglycine–xylidide test (MEGX) for formation of the lidocaine metabolite, and by bilirubin and AST, drug clearance is markedly reduced and significantly correlated only with MEGX and bilirubin. For vinorelbine, therefore, as for the other vinca alkaloids, dose reduction is recommended in patients with severe liver dysfunction, but not those with moderate liver involvement.

Taxanes, which enhance microtubule assembly and inhibit tubulin depolymerisation [65], are metabolised mainly through the liver and undergo biliary excretion [66]. Two main metabolites of paclitaxel, corresponding to hydroxylation at the C6 position of the taxane ring and at the *para* position of the phenyl ring at the C3 position of the C13 side chain, account for 70% of biliary excretion. A retrospective finding from preliminary reports by Egorin and associates [67] and Venook and associates [68] suggests that in patients with severely affected liver function (bilirubin higher than 3 mg/100 ml), the serum concentration of paclitaxel at the steady state is higher and the total body clearance after 24-h infusion lower than in patients with normal bilirubin.

Dose-limiting toxicity, mostly neutropenia, was observed in patients with high bilirubin levels. Similar results were obtained by Wilson and associates [69] in a phase II study with a 96-h infusion of paclitaxel in patients with liver metastases but bilirubin not higher than 2 mg/100 ml. Metastatic liver disease was strongly associated with reduced drug clearance, higher steady-state concentrations and increased haematological toxicity. The extent of liver involvement, evaluated by computed tomography, was inversely correlated with paclitaxel clearance. Therefore it was suggested that in patients with evidence of extensive liver metastases or liver disease with clearly abnormal liver function tests, the starting dose of paclitaxel should be reduced by 30%. This same report noted that serum levels of AST were significantly related to the presence of liver metastases. Therefore, the authors suggested that AST may be a better predictor of liver dysfunction and of decreased drug clearance than total bilirubin, which was not substantially altered in these patients. Seidman and associates [70] reduced the dose, which proved to be safe in metastatic breast cancer patients with hepatic dysfunction, as reflected by elevation of AST and ALT more than twice the upper limit of normal. The steady-state concentration of paclitaxel, which was twice as high as in patients with normal transaminases, was directly related to the incidence of grade 4 neutropenia, but there was no relationship between serum drug levels and response. However, further studies with a prospective design are clearly required.

As regards the neurotoxicity of paclitaxel, it is dosage-schedule dependent [71] and roughly correlates with the AUC [72]. However, appropriate clinical trials relating drug-induced neuropathy and pharmacokinetic parameters are not yet available.

The semisynthetic taxane analogue docetaxel has been investigated extensively in phase I and II population pharmacokinetic studies [73]. Although Bruno and associates [74] reported that drug clearance was correlated with plasma hepatic enzyme levels, in patients with 'elevated hepatic enzymes' a 30% reduction in clearance did not seem to modify significantly the toxic or therapeutic response. Hudis and associates [75] confirmed in 34 patients that the total drug availability as expressed by the AUC did not apparently correlate with toxicity. However, in this study 1 patient with hepatic metastases and pretreatment bilirubin of 1.8 mg/100 ml, resulting in a much higher steady-state level (11.6 μg/ml versus a median of 4.6 μg/ml for the other patients) and decreased docetaxel clearance, died with extensive haematological and non-haematological toxicity.

That the risk of toxicity (neutropenia and mucositis) with docetaxel increases with liver metastases and elevated AST and alkaline phosphatase serum levels has been previously observed [76]. Therefore, caution is warranted and dose reduction seems advisable for docetaxel when treating

patients with liver dysfunction, although the correlation between pharmacokinetic parameters and toxicity needs further investigation.

## EPIPODOPHYLLOTOXINS

The epipodophyllotoxins etoposide (VP16) and teniposide (VM26) are widely used antitumour compounds, whose pharmacokinetics in the presence of organ failure has been investigated. VP16 and VM26 in humans are cleared both by the kidneys and by direct hepatobiliary metabolism and excretion of the inactive glucuronide and sulphate derivatives [77]. Impairment of liver function may reduce the rate of metabolism and/or biliary excretion of these compounds, thus increasing toxicity. Therefore, in clinical practice in patients with elevated bilirubin the dose is often reduced. Dose reduction, however, may compromise achievement of the drug serum concentrations needed for optimal response to therapy. Slevin and associates [78] demonstrated that the therapeutic effect of etoposide is related to the presence of a critical drug level for a given time. Rodman and associates [79] established a similar relationship for VM26, showing good correlation between drug steady-state concentration or clearance and response rate in children.

Several studies are available on the pharmacokinetics of VP16 and VM26, administered intravenously to patients with primary or metastatic liver cancer or with liver dysfunction of different origin. Sinkule and associates [80] suggested that the decreased clearance and prolonged half-life of VP16 in four children with high serum transaminases might be attributable to the concomitant lower creatinine clearance induced by prior cisplatin treatment. Results of other studies are summarised in Table 6, with the pharmacokinetic parameters for comparison. Arbruck and associates [81], D'Incalci and associates [82] and Hande and associates [83] found neither decreased total body clearance nor prolonged half-life of total VP16 in patients with severe liver dysfunction (bilirubin often ten times normal) even when associated with obstructive jaundice, as the low liver metabolic clearance in these patients is compensated by an increase in renal clearance. Meta-analysis of the combined data [83] clearly indicates that the serum pharmacokinetics of the total drug is not significantly altered in the presence of liver impairment.

On the basis of the information outlined in these pharmacokinetic studies, normal i.v. doses of VP16 should be given to patients with liver dysfunction. However, caution should be used in patients with severe liver dysfunction and renal impairment, in whom the decrease in metabolic clearance cannot be compensated for by increased renal clearance.

Alternatively, an increased fraction of the unbound active drug directly related to high serum bilirubin and low albumin levels might explain the increased pharmacological and toxic effects (neutropenia) of standard VP16 doses in patients with liver disease [84]. Other authors [85], while confirming this finding for albumin, were not able to demonstrate a clear relationship between serum bilirubin levels and protein binding. Similar pharmacokinetic behaviour was reported for prolonged oral treatment with VP16 [86, 87]. The consideration that severe neutropenia may occur after prolonged oral treatment suggests that, apart from any pharmacokinetic consideration, it may be advisable to monitor neutrophil count often during oral VP16 treatment in patients with liver dysfunction.

Two papers describe the pharmacokinetics of the VP16 analogue, VM26 [88, 89]. In children with leukaemia, Canal and associates reported a significant inverse relationship between APH and systemic clearance of VM26, while in patients with ovarian carcinoma an inverse correlation was found between $\gamma$-GT and plasma clearance of the compound. However, these data come from small groups of patients whose clearance was only moderately reduced and, although they emphasise the role of the liver in drug clearance, they are not sufficient to establish dosage guidelines.

## DISCUSSION

The present review looks at the pharmacokinetics of selected anticancer agents in the presence of liver impairment. The aim was to assess whether guidelines for dose adjustments could be extrapolated from pharmacokinetic studies, but the conclusion is that in most instances the empirical dose adjustments that are still the rule in clinical practice are not justified by experimental data.

Conventional doses of anticancer drugs are established by phase 1 trials to fit the balance between optimal therapeutic effects and safety in the average population of patients. The need for dose adjustment is based on the recognition that individual patients may be different from 'normal' patients, so that standard doses may have lower efficacy or worse toxicity than expected. Patients with liver dysfunction clearly deviate from the norm in many ways, such as their total body clearance and disposition, that may affect key pharmacokinetic parameters of anticancer drugs and the pharmacodynamic consequences of their administration.

It would appear obvious that dose adjustments must be tailored on the basis of established relationships between specific indices of liver dysfunction and the ensuing pharmacokinetic alterations. However, guidelines are lacking since their definition depends both on the type and extent of liver disease, and on the unique characteristics of each drug. Guidelines can only be established by studying homogeneous patient populations in terms of diagnosis and by stratifying patients according to the severity of liver disease. However, these key criteria were not met in almost all the studies reviewed.

The case of the anthracyclines is typical in this respect [90]. In spite of years of technically adequate measurements of anthracycline pharmacokinetics, data were collected from patients in whom abnormal liver biochemistry was associated with different liver diseases, such as metastases, primary liver cancer or non-neoplastic liver diseases of different etiologies. Therefore, different studies often reported conflicting results. As a result, the dose of doxorubicin or epirubicin is still empirically adjusted, on the basis of serum bilirubin.

For the other major antineoplastic agents, the information available in the literature indicates that in patients with moderate liver dysfunction their clearance does not appear to be substantially modified. Therefore, dose reduction is not necessarily recommended, since it could lead to ineffective therapeutic levels. In fact, although caution is compulsory in treating patients with impaired organ function, considerations of the risks of toxicity should not compromise the achievement of therapeutic benefit.

For the vinca alkaloids, VCR, VLB and vinorelbine, there is strong evidence that dose reduction is mandatory in the presence of liver impairment, particularly severe impairment, and especially with cholestasis. Dose adjustment seems to be advisable also for the newer compounds paclitaxel and docetaxel, which are cleared more slowly in patients with ele-

*Table 6. Pharmacokinetics of etoposide in cancer patients with liver dysfunction*

| Year | Study | Dose mg/sq.m i.v. | Diagnosis No. with liver dysfunction/total | Indices of liver dysfunction | Pharmacokinetic behaviour | Authors' comments |
|---|---|---|---|---|---|---|
| 1986 | Arbruck [81] | 100 × 3 | Different carcinomas (8/17 hepatobiliary tumours) | Bil (2–10 × normal)<br>AST (2 × normal)<br>APH (2–5 × normal) | Cls (ml/min/sq.m.)<br>21.4 + 7.4 in C<br>22.4 + 9.6 in Ld<br>β $t_{1/2}$ (h)<br>8.1 + 2.8 in C<br>8.4 + 3.9 in Ld | No changes in etoposide kinetics in the presence of liver dysfunction. Dose reduction may not be required |
| 1986 | D'Incalci [82] | 80–150 × 1 or 3 | Hepatocarcinoma or extrahepatic tumours with/without liver metastases (15/33) | Bil (2–20 × normal, 9 pts)<br>$\gamma$-GT (3–20 × normal)<br>APH (2–7 × normal) | Cls (ml/min/sq.m)<br>22.8 + 1.0 in C<br>27.9 + 2.7 in Ld<br>β $t_{1/2}$ (h)<br>5.6 + 0.4 in C<br>5.4 + 0.6 in Ld | No changes in etoposide kinetics in the presence of liver dysfunction. However, in three patients with severe cholestasis clearance was low (> 87 ml/min/sq.m). Dose reduction may not be required except in presence of cholestasis |
| 1990 | Hande [83] | 100–800 | Obstructive jaundice in patients with cancer (11/33) | Bil (2–12 × normal)<br>AST (3–6 × normal)<br>APH (2–8 × normal) | Cls (ml/min/sq.m)<br>26.5 + 9.8 in C<br>24.5 + 6.5 in Ld<br>β $t_{1/2}$ (h)<br>6.4 + 2.5 in C<br>5.7 + 1.5 in Ld | No changes in etoposide kinetics in the presence of liver dysfunction. Standard doses should be used in patients with obstructive biliary disease |
| 1996 | Joel [84] | 500 | Small cell lung cancer (total 72 patients) | AST or $\gamma$-GT with albumin ≥ 35 g/l<br>mild (1.5–3 × normal, 3pts)<br>severe (> 3 × normal, 4 pts)<br>albumin < 35 g/l | AUC (μg/mlxh)<br>total 457, free 16.6<br>total 536, free 20.2<br>total 425, free 22.8<br>total 463, free 27.4 | No changes in the kinetics of total etoposide in the presence of liver dysfunction. However, severe liver dysfunction, even more with low albumin levels, results in an increase of the free drug and more pronounced haematological toxicity. Dose reduction is advisable in patients with low albumin |
| 1995 | Liu [85] | 50/mg day oral or i.v. | Different solid tumours and two lymphomas | Bil (2–10 × normal, 6 pts)<br>APH (1.5–12 × normal)<br>albumin (< 30 g/l, 12 pts) | | Free fraction of etoposide shows a strong negative correlation with serum albumin ($P < 0.0001$), but not with serum bilirubin |

See legends to Tables 1 and 2.
C, controls; Ld, liver dysfunction; Cls, systemic clearance; β $t_{1/2}$, β half-life.

vated bilirubin [67, 68, 75] or other liver enzymes such as AST and APH [69, 74, 76]. However, at present, only a reduction in clearance appears to be directly correlated with increased haematological toxicity and mucositis [70, 76] and no relationship has been found between serum drug levels and response [70, 74, 75].

A clinically important question is whether biochemical indices of liver dysfunction predict alterations in drug clearance. To our knowledge the only reports dealing with this are by Twelves and associates for epirubicin [34] and Wilson and associates [69] for paclitaxel. Evidence was provided that serum levels of AST, a good predictor of survival in cancer patients with liver metastases [91], may provide a more rational basis for dose adjustment in cancer patients treated with epirubicin or paclitaxel than the currently recommended bilirubin, which does not always show appreciable changes.

The same considerations may possibly apply to docetaxel [76], although the limited number and broad heterogeneity of the patients studied, as well as the uneven characterisation of the aetiology and severity of liver disease, do not permit any general conclusion. However, there is an interesting relationship between the extent of liver involvement and paclitaxel clearance in patients with metastatic breast cancer [69]. For patients with primary or secondary liver cancer, it would be useful to establish a relationship between the size of the tumour, which is easily measured by ultrasonography, and the changes in pharmacokinetic parameters. Studies specifically aimed at establishing such relationships are warranted, at least for drugs whose pharmacokinetics change in the presence of liver dysfunction. Various biochemical indices of liver impairment that might predict changes in drug pharmacokinetics should be further investigated. Parameters of liver dysfunction may be related to necrosis and inflammation (AST and ALT), to cholestasis (total and esterified bilirubin, bile acids, albumin, $\gamma$-GT), or to reduced hepatocellular mass leading to impairment of liver function (mainly the quantitative dynamic tests, such as those based on antipyrine or lidocaine metabolite formation or on galactose elimination capacity). Among the dynamic tests the relatively new MEGX test correlates with the liver histological status better than the other biochemical tests [64] and has some prognostic significance, as low MEGX levels were limited to poor survival [92].

To design specific studies aimed at establishing guidelines for dose adjustment of antineoplastic agents in patients with liver diseases, the type and degree of liver dysfunction must be clearly defined. Moreover, as severe liver disease is often associated with other structural and functional organ abnormalities such as renal impairment, the patients' general pathophysiological state must always be checked.

In conclusion, liver dysfunction is often associated with abnormal clearance of anticancer agents. Dose adjustment according to pharmacokinetic guidelines is needed in order to avoid the risk of undertreatment often associated with empirical criteria. Future clinical studies might assess relationships between markers of liver disease, disposition of anticancer agents and their safety in groups of patients homogeneous for aetiology and stratified for the degree of liver impairment.

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