Effect of Allyl Alcohol-induced Sublethal Hepatic Damage upon Doxorubicin Metabolism and Toxicity in the Rabbit

Dean E. Brenner, Lowell B. Anthony, Susan Halter, Nancy Lindsay Harris, Jerry C. Collins, and Kenneth R. Hande

Departments of Medicine [D. E. B., L. B. A., N. L. H., J. C. C., K. R. H.] and Pathology [S. H.], Nashville Veterans Administration Medical Center and Vanderbilt University, Nashville, Tennessee 37203

ABSTRACT

A model of hepatic dysfunction in vitro has been developed in rabbits to determine the effects of sublethal hepatocellular necrosis upon doxorubicin pharmacology. Eight New Zealand white rabbits were given 3 mg/kg doxorubicin i.v. Plasma doxorubicin and metabolite pharmacokinetics were determined and toxicity assessed by nadir complete blood counts. Hepatic function was assessed by the pulmonary excretion rate of \(^{14}C\)CO\(_2\) from \(^{14}C\)aminopyrine. Hepatocellular necrosis was produced by i.v. injection of 1.55 mg/kg of a 2% allyl alcohol solution. Doxorubicin administration and pharmacokinetics were repeated.

Doxorubicin enhances the hepatotoxicity of allyl alcohol. Hepatocellular necrosis does not alter the plasma pharmacokinetics of doxorubicin but does increase the plasma exposure of doxorubicinol. Doxorubicin-induced myelosuppression is enhanced by allyl alcohol pretreatment. These data suggest that in circumstances of reduced hepatocellular volume or acute hepatocellular necrosis, a key plasma marker of doxorubicin-induced acute toxicity may be doxorubicinol.

INTRODUCTION

Cancer patients receive multiple drugs during their treatment, many of which are either detoxified or excreted by the liver. Dox\(^1\), a major clinical antineoplastic agent, is reduced in cellular cytoplasm by aldehyde and ketone reductases (1–7) and detoxified in the hepatocyte most likely by NADPH cytochrome P-450 reductase catalyzed reduction of the oxygen linked glycoside to deoxyglycoside forms (8, 9) (Fig. 1). Dox and doxorubicinol are excreted unchanged by the liver and to a small extent (approximately 6%) in the urine (1, 3–5, 10, 11). Small amounts of aglycones are found circulating in human and in rabbit plasma (12).

Clinical-pharmacokinetic data from 8 patients suggested that moderate changes in hepatic function caused increased Dox toxicity reflected in altered pharmacokinetics (13, 14). Other studies have suggested that Dox pharmacokinetics and metabolism correlated with deranged hepatic function as measured by bromsulphothalein retention time (13), bilirubin (13, 15), or indocyanine green clearance (16); yet other work has failed to correlate drug-induced toxicity to pharmacokinetics (17–21).

We hypothesized that correlations of Dox pharmacokinetics with acute toxicity in humans have not been possible because (a) parent compound may not be the sole or optimal marker for drug activity or toxicity, (b) assay techniques were not sensitive enough to detect important metabolites, (c) there was insufficient knowledge about the activity and toxicity of Dox metabolites and, (d) there were too many uncontrolled variables in studied clinical populations. These variables include the effects of coadministration of drugs that are hepatically metabolized, variations in the degree of illness among cancer patients, and undefined clinical or subclinical hepatic disease which may alter drug pharmacokinetics and pharmacodynamics.

In order to control possible variables, we have developed the rabbit as an economically feasible animal model of Dox metabolism. This model has the advantage of repetitive blood sampling and repetitive drug administration in the same animal. Compared to rodents, Dox metabolism in the rabbit is closer to the human (1, 22, 23). In order to simulate acute hepatic dysfunction, we induced sublethal hepatic lesions in rabbits with allyl alcohol. We then evaluated Dox pharmacokinetics, metabolism, hepatic function, and toxicity in paired studies with allyl alcohol-induced hepatic lesions. These studies were performed in the rabbit to determine, in a controlled model, whether pharmacokinetics affected the toxic ongoing events in the liver and whether they predicted pharmacodynamic changes as measured by myelosuppression. These lesions caused a small increase of Dox AUC and an increase of Doxol AUC. Myelotoxicity was enhanced by allyl alcohol pretreatment.

MATERIALS AND METHODS

Materials. Doxorubicin hydrochloride was purchased as commercial material from Adria laboratories. Tetrahydrofuran was obtained from Fisher Laboratories of Allied Industries, Inc. and was HPLC grade. Ammonium formate (Fisher certified) buffer, 0.1% (v/v) (16 mm) was made daily with distilled water adjusted to pH 4.0 with formic acid (Fisher certified). The buffer was subsequently filtered and degassed using a 0.45-μm filter (Millipore, Milford, MA) before use. For chemical extraction, chloroform (Fisher certified), and ammonium sulfate (Fisher certified) were used. Allyl alcohol (J. T. Baker Chemical Co., Phillipsburg, NJ) was diluted in filtered 0.9% saline solution to a 2% concentration before use. \(^{14}C\)aminopyrine (\(^{14}C\)aminopropylidene); specific activity, 90–100 mCi/mmol) was obtained from Research Products International Corp., Mt. Prospect, IL. Aquasol was obtained from New England Nuclear, Boston, MA.

Synthesis of Dox Metabolites. The following metabolites were synthesized according to the published procedures of Takanashi and Buchar (24): Doxl; doxorubicin aglycone; doxorubicinol aglycone; 7-deoxydoxorubicin aglycone; and 7-deoxydoxorubicin aglycone. Identity of the standards was confirmed by negative ionization mass spectrometry using a Nermag R-10-10-B quadrupole mass spectrometer equipped with a Sidar 110 data system. Purity of all standards was confirmed by a single peak on HPLC at published retention times (12). The lack of other peaks in the HPLC trace at the sensitivity used suggested at least 95% purity.

Rabbits. Female, white, New Zealand rabbits, 3–4 kg were obtained from a local supplier of laboratory rabbits (Myrrles, Eagleville, TN) and maintained in clean, individual cages in the animal quarters at the Nashville Veterans Administration Medical Center. The animals were certified Pasteurella and disease free upon receipt and were kept in a separate clean room from other rabbits. The quarters are supervised by the local Animal Care Committee as required by United States Federal regulations under the supervision of a veterinarian. Study procedures were reviewed by the veterinarian and the local Research and Development Committee prior to the study. Care was taken to minimize animal discomfort.

Received 11/11/86; revised 3/10/87; accepted 3/19/87.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertised in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This investigation was supported by the Veterans Administration, Clinical Research Center Grant RR 0095, American Cancer Society Institutional Grant IN25V, and NIH BRSG-RR-05425.

2 To whom requests for reprints should be addressed, at Department of Clinical Pharmacology and Therapeutics, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY, 14263.

3 The abbreviations used are: Dox, doxorubicin; Doxl, doxorubicinol; AUC, area under the curve; HPLC, high pressure liquid chromatography; CBC, complete blood count; HPF, high powered field; \(K_{el}\), elimination rate constant.

3259
LIVER DAMAGE AND Dox METABOLISM

![Chemical structure of doxorubicin and its metabolites](image)

Fig. 1. Proposed metabolic schema of doxorubicin metabolism (modified and reprinted by permission from Ref. 39).

Table 1. Schema of study

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
<th>32</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (n = 8)</td>
<td>3 mg/kg</td>
<td>3 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allyl alcohol*</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic study</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[14C]Aminopyrine breath test</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Administration of 1.35 ml/kg of a 2% allyl alcohol solution i.v.
* Three-mI blood specimens were drawn after doxorubicin administration at 5 and 15 min and 1, 2, 4, 8, 12, 24, 36, 48, and 72 h. Complete blood counts were obtained on days 1, 5, 6-9, 28, and 33-37. Animals were sacrificed as described in the text. After the second WBC nadir, livers were removed fresh, fixed, and processed.

The rabbits were fed ad libitum and allowed unlimited water supply. The animals were sacrificed by intracardiac injection of 1 ml of T-61 euthanasia solution (Hoechst, Sommerville, NJ) which caused death within 15 s of injection.

Experimental Procedure. Eight rabbits were treated according to the schema in Table 1. The blood was immediately centrifuged at 4°C. The plasma supernatant was removed and frozen at −20°C until assay.

Pharmacokinetics. Doxorubicin plasma concentrations were fit by a noncompartmental method (27) using a noncompartmental method (27)

\[ C_{0} = A e^{-t/\alpha} + B e^{-t/\beta} \]

where \( C_{0} \) is the plasma concentration at time \( t \), \( A \) and \( B \) are constants, and \( \alpha \) and \( \beta \) are linear elimination rate constants. A 1/(concentration)^2 weighting function was used for curve fitting. The AUC was calculated for Dox by the log-trapezoidal rule to infinity. Clearance was calculated by

\[ D_{a} \times \text{AUC} \]

where \( D_{a} \) is the administered dose. Volume of distribution was calculated by

\[ V_{d} = D_{a} \times \text{AUMC/AUC} \]

RESULTS

[14C]Aminopyrine Breath Test. The [14C]aminopyrine breath test was adapted to rabbits from the technique used in the rat (28) to provide sensitive measurement of hepatic function. Using this technique we have found that the [14C]aminopyrine half-life is prolonged in the rabbits as they gained weight from 2.5-3.0 kg. We attributed this increase to the maturation from juvenile to adult hepatic function. Over a subsequent 4-month period the Ka and half-life stabilized with little variability within rabbits but substantial variability between rabbits. Additional work has documented increases in half-life in the presence of...
**LIVER DAMAGE AND DOX METABOLISM**

Table 2  Doxorubicin pharmacokinetic parameters (n = 8)

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>No pretreatment AUC (μmol × h)</th>
<th>Terminal half-life (h)</th>
<th>Cₚ₀ (μmol)</th>
<th>Cₜμ (liter/min/kg)</th>
<th>Vₘ (liter/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pretreatment</td>
<td>2.03 ± 1.25*</td>
<td>23.1 ± 9.8</td>
<td>0.37 ± 0.27</td>
<td>0.058 ± 0.027</td>
<td>91.1 ± 49.9</td>
</tr>
<tr>
<td>Allyl alcohol pretreatment</td>
<td>3.06 ± 2.28</td>
<td>28.8 ± 12.4*</td>
<td>0.41 ± 0.22</td>
<td>0.060 ± 0.068</td>
<td>87.9 ± 46.9</td>
</tr>
</tbody>
</table>

* Mean ± SD.

commonly used microsomal inhibitors such as cimetidine and decreases in half-life in the presence of commonly used microsomal inducers (phenobarbital). These data are presented in a separate communication. Because of substantial variation among rabbits, [¹⁴C]aminopyrine breath test data are presented as a ratio of experimental to control. Each rabbit served as its own control.

A series of 3 control determinations was performed before drug administration. A separate group of 4 rabbits served as allyl alcohol alone controls. These animals were given allyl alcohol, 1.35 ml/kg of a 2% allyl alcohol solution. They received daily [¹⁴C]aminopyrine breath tests and CBCs until sacrifice 10 days after allyl alcohol administration. Three groups of studies were compared, rabbits treated with Dox alone, the same group of rabbits pretreated with allyl alcohol and Dox, and the third, a separate group of animals treated with allyl alcohol alone. Allyl alcohol alone caused a significant increase in the [¹⁴C]-aminopyrine half-life ratio compared to control (Fig. 2). The maximum increase occurred 24 h after allyl alcohol injection. By 96 h after injection, hepatic function had recovered sufficiently to reduce the ratio to control levels. Treatment with Dox alone did not cause significant changes in [¹⁴C]aminopyrine excretion over pretreatment control values. The addition of Dox to allyl alcohol caused the [¹⁴C]aminopyrine half-life ratio to increase in some but not all animals compared to allyl alcohol alone (Fig. 2). The changes lasted 2 days and returned to baseline by day 4.

Dox and Metabolite Pharmacokinetics. Dox pharmacokinetic data are listed in Table 2. No significant changes in Dox area under the curve, clearance, or volume of distribution were found in the paired studies. The terminal half-life was prolonged in the allyl alcohol pretreatment study. This difference is not large enough to have substantial effects on other important parameters of parent compound systemic exposure or elimination.

Evaluation of the metabolite data reveals increased exposure to the metabolite, Doxol (Table 3; Fig. 3). This increase was present in all but one of the rabbits treated. The degree of increase in the Doxol area under the curve varied markedly among the animals. This is reflected in the large S.D. The area under the curve of the other major metabolite detected, 7-deoxydoxorubicin aglycone, was unchanged by the allyl alcohol pretreatment. Small amounts of doxorubicin aglycone were detected for short periods of time immediately after drug injection. 7-Deoxydoxorubicin aglycone was intermittently detected in some rabbits in the first h after injection but became undetectable after the first h. In the majority of rabbits, 7-deoxydoxorubicin aglycone was not detected in either Dox alone or allyl alcohol pretreatment studies. Two nonpolar, unidentified proposed metabolites, arbitrarily labeled “C” and “G” (12) were consistently detected in low concentrations in the rabbits when they received Dox alone or Dox after allyl alcohol pretreatment. Allyl alcohol pretreatment did not affect the areas under the curve of these proposed metabolites (Table 3).

Previous human Dox pharmacokinetic studies suggested that the ratio of Dox to Doxol AUC reversed from less than 1.0 in patients with normal hepatic function to greater than 1.0 in patients who had hepatic dysfunction (19). We saw the same phenomenon in the rabbit studies presented here.

**Table 3**  Dox metabolite areas under the curve (n = 8)

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>No pretreatment (μmol/h)</th>
<th>Pretreatment with allyl alcohol (μmol/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>1.29 ± 0.92*</td>
<td>5.27 ± 2.88*</td>
</tr>
<tr>
<td>7-Deoxydoxorubicin</td>
<td>1.10 ± 1.47</td>
<td>1.69 ± 1.41</td>
</tr>
<tr>
<td>aglycone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;C&quot;</td>
<td>0.30 ± 0.12</td>
<td>0.21 ± 0.17</td>
</tr>
<tr>
<td>&quot;G&quot;</td>
<td>0.34 ± 0.35</td>
<td>0.45 ± 0.25</td>
</tr>
</tbody>
</table>

* Mean ± SD.

**Table 3**  Dox metabolite areas under the curve (n = 8)

The liver parenchyma of the control rabbits maintained the normal hepatic architecture with portal tracts, central veins, and liver plates composed of one layer of hepatocytes (Fig. 4, top). The majority of these animals had no evidence of degeneration. The liver tissue from 3 of the 8 control rabbits had a diffuse, fine vacuolization of the cytoplasm, defined as 1+ degeneration, but no control animal had large cytoplasmic vacuoles. Necrosis was seen in the liver tissue of only one of the control rabbits. This was characterized by single acidophil bodies located nonspecifically within the lobule. Degeneration was seen in the liver tissue of 6 of the 8 treated rabbits (Fig. 4, middle). Degeneration in these animals was characterized by cloudy swelling, which appeared as a diffuse, fine vacuolization of the cytoplasm, or by the presence of large vacuoles in the cytoplasm which did not displace the nucleus. In 4 of the 8 treated rabbits the degeneration was located around the central vein, and in 2 animals it involved the entire lobule in a diffuse pattern. Evidence of spotty necrosis (Fig. 4, bottom) was seen in all treated rabbits. No massive necrosis was seen in any of the animals.

Comparison of the degree of degeneration and necrosis in the liver of the control and treated rabbits is listed in Table 5. The treated animals had a statistically significant increase in the extent of degeneration and necrosis when compared with Student’s t test.

DISCUSSION

The rabbit model reported here provides important information that is unobtainable in human studies. Controlled,
Fig. 4. Upper, low power photomicrograph of the liver from a control rabbit. Note the liver plates (arrow) are one cell layer thick and the cytoplasm of the cells is homogeneous. H & E; bar, 300 μm. Middle, low power photomicrograph of the liver from a rabbit treated with allyl alcohol and Dox. Note vacuolization of the hepatocytes (arrow) which extends from the central vein (C) to the portal tract (P). The normal hepatic architecture is disrupted and the liver plates are expanded. H & E; bar, 300 μm. Lower, higher power detail of hepatocytes from the same rabbit liver pictured in middle section. Note the fine vacuolization in some hepatocytes (short arrow) and larger vacuoles in other liver cells (long arrow). Acidophil bodies (arrowhead) were located nonspecifically within the lobule. H & E; bar, 100 μm.
LIVER DAMAGE AND DOX METABOLISM

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Histological evaluation of liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See text for source of control and treated animals.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Extent of degeneration</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.75 ± 2.712</td>
<td>0.125 ± 0.354</td>
</tr>
<tr>
<td>Control + allyl</td>
<td>2.714 ± 2.563</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Treated</td>
<td>5.857 ± 3.042</td>
<td>1.00 ± 0*</td>
</tr>
</tbody>
</table>

* Mean ± SD.
* Differs from control group, at P < 0.05.
* Grading system: Degeneration, scale of 1–3, fine cytoplasmic vacuolation (Grade 1) to vacuoles of a size occupying the entire cytoplasm (Grade 3); Degree of Degeneration, scale of 1–4, 1–2 cell layers (Grade 1) involved to diffusely involved liver lobule (Grade 4); Extent of Degeneration, degeneration and degree of degeneration; Necrosis, scale of 1–4, 1–2 acidoophil bodies/10 high power fields (Grade 1) to greater than 10 acidoophil bodies/10 high power fields (Grade 4).

Targeted modifications in hepatic function such as specific chemical enzyme inhibition or toxic injury (29) may be studied without the difficulties of drug-drug interactions associated with the treatment of ill cancer patients requiring polypharmacy. The data obtained from the rabbit model may point to correlations of specific hepatic pathology and alterations of drug metabolism and toxicity.

The adaption of the [14C]aminopyrine breath test to rabbits provides the model with an important measure of hepatic function. In this study, the breath test demonstrated both the degree and length of time of deranged hepatic function after allyl alcohol administration. Dox by itself does not appear to cause changes in hepatic function. In combination with a hepatotoxin such as allyl alcohol, Dox enhances the derangement in hepatic function in most but not all animals. Since allyl alcohol is thought to exert its toxicity by the formation of intracellular free-radical adducts (30, 31), Dox may enhance allyl alcohol-induced hepatotoxicity due to the depletion of sulfhydryl scavenger molecules by a mechanism similar to the reported Dox-acetaminophen interaction (32).

The paired studies reported here suggest that measurement of plasma Dox concentrations alone in the setting of moderate hepatic dysfunction will not provide important information regarding likelihood of important drug-induced myelotoxicity. Dox plasma concentrations and pharmacokinetic analysis, with the exception of a small prolongation of terminal half-life, were not statistically changed after pretreatment with allyl alcohol compared to control values. Allyl alcohol pretreatment induced increased myelotoxicity compared to the paired control. Doxol concentrations were consistently elevated in the animals after allyl alcohol pretreatment. These elevations were reflected in the significant increase in the Doxol AUC compared to control values. Other aglycone metabolites were not as affected by hepatic dysfunction as were Doxol concentrations.

The enhanced Dox acute myelotoxicity observed in the allyl alcohol pretreatment study when compared to the paired controls is not artifactual: (a) the same volume of blood was obtained from the animals for each of the paired studies; (b) the pretreatment baseline CBC for the allyl alcohol study was the same as that for the Dox baseline study; (c) in a similarly designed paired study of a separate group of animals receiving ranitidine as a microsomal inhibitor, no differences in CBCs were found in the animals after a second course of Dox separated by a 4-week interval; (d) 4 animals as described previously were treated with allyl alcohol alone at the same dose given the animals in this study. After 10 days of consecutive CBCs, no change in any of the parameters from control were found (data not shown).

These data suggest that Doxol concentrations may play an important role in the definition of drug-induced myelotoxicity and may serve as an important predictive marker of drug-induced toxicity. This postulate is supported by other data. Chan et al. (19) after studying doxorubicin pharmacokinetics in hepatoma patients, found that noncirrhotic patients had Dox concentrations below those of Dox and had minimal drug-induced toxicity, whereas those patients with cirrhosis had elevated Doxol concentrations and increased drug-induced toxicity. Doxol is less cytotoxic in vitro to human myeloid progenitors (33–35) and pancreatic cancer cell lines (36) than Dox, yet it is functionally more cardiotoxic than Dox (37).

Based upon the metabolism of Dox, Doxol should be an important marker of drug toxicity. The aldehyde and ketone reductases that reduce doxorubicin to doxorubicinol are ubiquitous and probably not affected by reduction in hepatocellular volume or function (6, 7). Hepatic NADPH cytochrome P-450 reductase may be rate limiting with Dox detoxification (38). We hypothesize that in the setting of hepatic cellular necrosis, the detoxification of Dox to 7-deoxydoxorubicinol aglycone is more likely to be inhibited than the reduction of Dox to Doxol. If Doxol at physiological concentrations is more toxic than previously understood, as some of our preliminary pharmacological and toxicological data support, or if hepatic NADPH cytochrome P-450 reductase is rate limiting for drug detoxification, then in circumstances of reduced hepatocellular volume or acute necrosis, a key plasma marker of Dox-induced acute toxicity may be Doxol.

The data produced in a tightly controlled animal model of Dox metabolism may be applicable to human studies but would require verification in a clinical trial. Assay of Dox and metabolite pharmacokinetics following an initial dose in humans may provide important guidelines for upward or downward adjustment of dose in an individual. It would be ideal to have an inert marker that clinically predicts doxorubicin pharmacodynamics. Evidence that such markers (such as aminopyrine, indocyanine green) are of clinical value is lacking. The rabbit model may provide such evidence that will allow the design of rational clinical trials to answer these important questions.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Ian Blair for performing mass spectrometry, Rita Bennett for her technical assistance, Carol Smith for performing the chemistry assays, and Marty Courtney for manuscript preparation.

REFERENCES


3264
LIVER DAMAGE AND Dox METABOLISM

9. Oki, T., Komiyama, T., Tone, H., and Inui, T. Reductive cleavage of anthra-
cycline glycosides by microsomal NADPH cytochrome C reductase. J. An-
10. Tavoloni, N., and Guarino, A. M. Bile secretory function: a determinant of
11. Wilkinson, P. M., Israel, M., Pegg, W. J., and Frei, E. Comparative metab-
olism and excretion of Adriamycin in man, monkey, and rat. Cancer Chem-
12. Brenner, D. E., Galloway, S., Cooper, J., Noone, R., and Hande, K. R. Im-
proved high performance liquid chromatography assay of doxorubicin:
comparison of thin layer chromatography. Cancer Chemother. Pharmacol.,
13. Benjamin, R. S., Wiernik, P. H., and Bachur, N. R. Adriamycin chemother-
apy—efficacy, safety and pharmacologic basis of an intermittent single high
14. Reich, S. D., and Bachur, N. R. Alterations in Adriamycin efficacy by
15. Benjamin, R. S. A practical approach to Adriamycin toxicity. Cancer Chem-
16. Doroshow, J., and Chan, K. Relationship between doxorubicin clearance and
indocyanine green dye pharmacokinetics in patients with hepatic dysfunction.
1268, 1980.
20. Chlebowski, R. T., Chan, K. K., Tong, M. J., et al. Adriamycin and methyl-
CCNU combination therapy in hepatocellular carcinoma: clinical and phar-
doxorubicin toxicity: relationship to pretreatment liver function, response
and pharmacokinetics in patients with acute non-lymphocytic leukemia.
23. Maniez-Devos, D. M., Baurain, R., Trouet, A., and Lesne, M. Doxorubicin
25. Benjamin, R. S., Riggs, C. E., and Bachur, N. R. Plasma pharmacokinetics
of Adriamycin and its metabolites in humans with normal hepatic and renal
27. Benet, L. Z., and Babeazzi, R. L. Noncompartamental determination of the
28. Desmond, P. V., Branch, R. A., Calder, I., and Schenker, S. Comparison of
[14C]phenacetin and ainom[14C]pyrine breath tests after acute and chronic
29. James, R., Desmond, P., Kupfer, A., Schenker, S., and Branch, R. A. The
differential localization of various drug metabolizing systems within the rat
liver lobule as determined by the hepatotoxins allyl alcohol, carbon tetra-
of allyl alcohol metabolism in portalportal and pericentral regions of the liver
enhancement by a combination of drugs which deplete hepatic glutathione
209, 1980.
33. Ozols, R. F., Wilson, J. K. V., Weltz, M. D., Grotzinger, K. R., Myers, C.
E., and Young, R. C. Inhibition of human ovarian cancer colony formation
34. Yesair, D. W., Thayer, P. S., McNitt, S., and Teague, K. Comparative
uptake, metabolism and retention of anthracyclines by tumors growing in
metabolites to human marrow erythroid and myeloid progenitors in vitro.
1985.
of rat, rabbit and human liver NADPH-cytochrome P450 reductases. Bio-
Effect of Allyl Alcohol-induced Sublethal Hepatic Damage upon Doxorubicin Metabolism and Toxicity in the Rabbit


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/47/12/3259

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.