Reversal of Multidrug Resistance by Lipophilic Drugs

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ABSTRACT

The phenomenon of multidrug resistance implies that a wide spectrum of structurally and functionally unrelated chemotherapeutic drugs are recognized and processed by the molecular system which protects multidrug-resistant (MDR) cells against lipophilic cytotoxic drugs. This suggests that lipophilic agents with low toxicity may also be recognized and processed by this molecular system. At high concentrations these agents might saturate the system, thereby reversing multidrug resistance. In support of this hypothesis, 19 (73%) of 26 arbitrarily chosen lipophilic drugs were in this study found to increase the accumulation of actinomycin D in MDR WEHI 164 cells. The most potent of these drugs were also shown to sensitize these cells to the cytotoxic effect of actinomycin D and doxorubicin. There was a good correlation between the ability of the agents to reverse drug resistance and the ability of the agents might saturate the system, thereby reversing multidrug resistance. At high concentrations these agents were exposed to lipophilic drugs, and their ability to reverse drug resistance appeared to be additive, since increased accumulation of actinomycin D was shown to sensitize these cells to the cytotoxic effect of chemotherapeutic drugs. The ability to reverse drug resistance appeared to be additive, since increased accumulation of actinomycin D was obtained at reduced actinomycin D concentrations.

INTRODUCTION

Cancer chemotherapy often results in the emergence of multidrug-resistant tumor cells. This means that the cells have become not only resistant to the drug(s) being used in therapy but also cross-resistant to a wide spectrum of other chemotherapeutic drugs (1–3). An analogous in vitro situation is the emergence of MDR cells after culture of drug-sensitive cells in the presence of a lipophilic cytotoxic drug (3–9). Multidrug resistance appears to a large extent to be due to the overexpression of a membrane-associated glycoprotein (P-glycoprotein) which pumps drugs out of MDR cells, thereby preventing accumulation of drugs in the cells (3, 6–9).

The phenomenon of multidrug resistance implies that a wide spectrum of structurally and functionally unrelated lipophilic drugs are recognized and processed by the molecular system, presumably the P-glycoprotein, which protects MDR cells against lipophilic cytotoxic drugs. This suggested to us that nontoxic lipophilic agents may also be recognized and processed by this molecular system, and at high concentrations they might, consequently, saturate the system and thereby reverse multidrug resistance (10). Many commonly used antibiotics are lipophilic and much less toxic to the host than chemotherapeutic drugs. As a consequence we tested the effect of the antibiotic erythromycin on multidrug resistance and showed that erythromycin reversed the resistance of MDR cells to the chemotherapeutic drugs doxorubicin and actinomycin D (10).

MATERIALS AND METHODS

Cells and Culture Conditions. Actinomycin D-resistant cells were derived from WEHI 164 murine fibrosarcoma cells (13) (in this communication termed WEHI 164 parental cells or P-WEHI 164 cells) by culturing the P-WEHI 164 cells in the presence of actinomycin D (10). The resulting cells (termed act-R-WEHI 164 cells) had become not only more resistant to actinomycin D but also more resistant to doxorubicin, mitomycin, vincristine, and cycloheximide (10). The P-glycoprotein was overexpressed in these cells (11).

The act-R-WEHI 164 cells were cloned by limiting dilution in microwells (No. 3596; Costar, Cambridge, MA). In one cloning experiment 22 clones were picked and tested for resistance to actinomycin D and doxorubicin. Six of the clones were chosen on the basis of their resistance to actinomycin D and doxorubicin and allowed to expand in the absence of drugs, and samples were frozen and stored. Two of these clones, clone 19 and 20 (termed act-R(CL19)-WEHI 164 and act-R(CL20)-WEHI 164, respectively), were used in this study. All the WEHI 164 cell types were maintained as stationary cultures in RPMI 1640 (Gibco, Paisley, United Kingdom) containing 10% fetal calf serum (Gibco), 2.7 mM l-glutamine, and 40 µg/ml gentamicin. The culture medium was changed every 3–4 days.

Drugs. Actinomycin D was purchased from Sigma, St. Louis, MO, and doxorubicin from Farmitalia, Milan, Italy. Erythromycin was from Abbott, Queensborough, United Kingdom; propranolol from AL, Oslo, Norway; furosemide from Alfred Benzon, Copenhagen, Denmark; lidocaine and cloxacinill from Astra, Sädertalje, Sweden; pirenzepine from Boehringer Ingelheim, Ingelheim, Federal Republic of Germany; indomethacin and chlorpromazine from Dumex, Copenhagen, Denmark; salbutamol and ceftazidime from Glaxo, Greenford, United Kingdom; cefotaxime from Hoechst, Frankfurt, Federal Republic of Germany; biperiden from Knoll, Ludwigshafen, Federal Republic of Germany; amitriptyline from Lundbeck, Copenhagen, Denmark; phenobarbital, morphone, pethidine, and trimethoprim from NAF, Oslo, Norway; phenytoin, verapamil, and calcium folinate from Nycomed, Oslo, Norway; chlorpromazine and promethazine from Rhône-Poulenc, Paris, France; midazolam from Roche, Basel, Switzerland; netilmicin from Schering Corp., Kenilworth, NJ; potassium canrenoate from Searle, Old Orchard, IL; clindamycin and hydrocortisone from Upjohn, Kalamazoo, MI; and pentazocine from Winthrop, New York, NY.

Colorimetric MTT Cytotoxicity Assay. The MTT cytotoxicity assay (14) was used to measure the cytotoxic effect (15). Target cells (1 or 2 x 10⁴ cells in 100 µl complete medium when cells were subsequently incubated for 48 or 24 h, respectively) were added to 6-mm microculture wells (Costar 3596) together with various amounts of lipophilic drugs and human recombinant TNF (provided by Knoll/BASF). The final volume in each well was adjusted to 110 µl. After 48 or 24 h of incubation at 37°C, 10 µl MTT at a concentration of 5 mg/ml in phosphate-buffered saline was added to each well and the cells were incubated for an additional 4 h. The MTT is reduced by living cells to an orange formazan that is solubilized in DMSO and measured spectrophotometrically at 570 nm. A 48% inhibition of the formazan production was considered to indicate activity. In the experiments the cells were incubated for 48 h except where otherwise specified.
saline, pH 7.2, were added. The cultures were then incubated for 4 h at 37°C, after which 50 μl of the supernatant were removed and replaced with 100 μl of 0.04 M HCl in isopropyl alcohol. After the dark blue formazan had dissolved, the absorbance of each well was measured with a Dynatech MR 600 Microplate reader using a test wavelength of 570 nm and a reference wavelength of 630 nm. The percentage of cytotoxicity was calculated as

\[ \frac{\text{absorbance in wells with drugs/TNF}}{\text{absorbance in control wells without drugs/TNF}} \times 100 \]

**Assay for Measuring Drug Accumulation in Cells.** Cells (4 × 10⁴ in 100 μl complete medium) were seeded into 6-mm microculture wells (Costar 3596) and incubated for 4 h at 37°C in order to obtain adherent cells. Thereafter 0.5 μCi of [³H]actinomycin D (specific activity, 4.6 Ci/mmol; Amersham, Little Chalfont, United Kingdom) were added per well together with various concentrations of lipophilic drugs. After further incubation for 4 h at 37°C, the cells were trypsinized [0.25% trypsin (Gibco), 2 min, 37°C] and harvested with a TiterTek multiple cell harvester; then radioactivity was determined. Background radioactivity (200–500 cpm) has been subtracted in all data shown.

**Statistics.** Results are given as mean ± SD of quadruplicate (for cytotoxic data) or triplicate (for drug accumulation data) determinations from single experiments.

**RESULTS**

**Accumulation of Actinomycin D in MDR Cells in the Presence of Lipophilic Drugs.** To test the hypothesis that multidrug resistance implies that a wide spectrum of unrelated lipophilic drugs may interfere with drug resistance, 26 arbitrarily chosen lipophilic drugs were screened for their ability to increase the accumulation of actinomycin D in the MDR act-R(C1.20)-WEHI 164 cells. Their potency in doing so was compared to that of erythromycin and verapamil, all the drugs are listed in Table 1 in order of increasing effect of accumulation of actinomycin D in the MDR cells. The potency of propranolol, amitriptyline and potassium canrenoate were extremely significant (P < 0.01) increase in the accumulation of actinomycin D in the MDR cells at drug concentrations less than those shown in Table 1 was determined (Fig. 1). An increased accumulation of actinomycin D was detected at drug concentrations between 1 and 10 μg/ml (100% accumulation at 20–30 μg/ml for propranolol, verapamil, amitriptyline, potassium canrenoate, and propranolol and 50–100 μg/ml for pentazocine) (Fig. 1). For all drugs tested, there was a 10-fold difference between the lowest drug concentration where an effect on the accumulation of actinomycin D was detected and the concentration where an accumulation of 100% was obtained.

For a lipophilic agent to be clinically useful in reversing drug resistance it must have low in vivo toxicity at the concentrations where it effectively reverses drug resistance. Since various drugs may exert their toxic effects differently, interfering with different physiological and/or cellular processes, the toxic effect in vivo of two or more drugs may be less than additive. One might, however, expect that their ability to induce an increased accumulation of actinomycin D in MDR cells is additive. To investigate this hypothesis, we tested whether a mixture of 5 lipophilic drugs, the concentration of each drug being chosen to be on the average one-fifth of that required for the drug alone to induce 100% accumulation of actinomycin D, could effectively increase the accumulation of actinomycin D in the MDR cells (Fig. 2). In the absence of the lipophilic drugs the accumulation of actinomycin D in the MDR cells was 12% of that in the drug-sensitive parental cells. This increased to between 20 and 40% when each of the lipophilic drugs used in the mixture (amitriptyline, promethazine, pentazocine, verapamil, and propranolol) was present alone (Fig. 2). In the presence of the drug mixture, the accumulation of actinomycin D in the MDR cells was nearly that of the drug-sensitive parental cells (Fig. 2). An accumulation of 68% was obtained when the mixture contained only the three drugs amitriptyline, verapamil, and propranolol.

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**Table 1** Effect of lipophilic drugs on accumulation of actinomycin D in MDR cells

<table>
<thead>
<tr>
<th>Lipophilic drug</th>
<th>Lipophilic drug conc. (μg/ml)</th>
<th>% of accumulation of actinomycin D in clone 20 cells *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>21 ± 2*</td>
<td>18 ± 1 17 ± 1</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>20 ± 3</td>
<td>19 ± 2 23 ± 3</td>
</tr>
<tr>
<td>Pirenzepine</td>
<td>21 ± 1 20 ± 2 20 ± 1</td>
<td>21 ± 1 25 ± 1</td>
</tr>
<tr>
<td>Furosemide</td>
<td>21 ± 1 23 ± 1 22 ± 1</td>
<td>21 ± 1 25 ± 1</td>
</tr>
<tr>
<td>Calcium folinate</td>
<td>21 ± 1 24 ± 1 22 ± 1</td>
<td>21 ± 1 25 ± 1</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>21 ± 2</td>
<td>24 ± 1 26 ± 2</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>21 ± 1</td>
<td>25 ± 1 25 ± 1</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>20 ± 3</td>
<td>26 ± 1 30 ± 2</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>21 ± 7</td>
<td>29 ± 6 102 ± 1</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>21 ± 2 26 ± 2 35 ± 2</td>
<td>21 ± 2 35 ± 2</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>20 ± 3</td>
<td>40 ± 2 107 ± 1</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>21 ± 1 21 ± 1 41 ± 1</td>
<td>21 ± 1 41 ± 1</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 ± 3</td>
<td>42 ± 2 68 ± 8</td>
</tr>
<tr>
<td>Midazolam</td>
<td>20 ± 3</td>
<td>46 ± 5 53 ± 4</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>18 ± 3</td>
<td>17 ± 2 47 ± 7</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>18 ± 3 22 ± 1 50 ± 8</td>
<td>18 ± 3 50 ± 8</td>
</tr>
<tr>
<td>Morphine</td>
<td>20 ± 3</td>
<td>54 ± 5 112 ± 4</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>13 ± 2 50 ± 3 79 ± 9</td>
<td>13 ± 2 79 ± 9</td>
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<tr>
<td>Pethidine</td>
<td>18 ± 3 33 ± 3 88 ± 7</td>
<td>18 ± 3 88 ± 7</td>
</tr>
<tr>
<td>Biperiden</td>
<td>20 ± 3</td>
<td>122 ± 2 110 ± 24</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>20 ± 3 36 ± 2 133 ± 168 ± 29</td>
<td>20 ± 3 133 ± 29</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>20 ± 3 66 ± 4 218 ± 37</td>
<td>20 ± 3 218 ± 37</td>
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<tr>
<td>Pentazocine</td>
<td>18 ± 3 90 ± 1</td>
<td>18 ± 3 90 ± 1</td>
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<tr>
<td>Promethazine</td>
<td>18 ± 3 94 ± 7</td>
<td>18 ± 3 94 ± 7</td>
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<tr>
<td>Verapamil</td>
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<tr>
<td>Potassium canrenoate</td>
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<td>20 ± 3 182 ± 5</td>
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<tr>
<td>Amitriptyline</td>
<td>21 ± 1 265 ± 10</td>
<td>21 ± 1 265 ± 10</td>
</tr>
<tr>
<td>Propranolol</td>
<td>21 ± 1 265 ± 4</td>
<td>21 ± 1 265 ± 4</td>
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</tbody>
</table>

* A 100% accumulation of actinomycin D was defined as the amount of actinomycin D which accumulated in the parental WEHI 164 cells in the absence of lipophilic drugs.

**a** Mean ± SD.

**b** Drug concentration not tested.
Fig. 1. Effect of lipophilic drugs on the accumulation of actinomycin D in P-WEHI 164 cells (●) and act-R(C1.20)-WEHI 164 cells (○). Cells were cultured for 4 h with the indicated amounts of the different lipophilic drugs and actinomycin D, before drug accumulation was measured as described in “Materials and Methods.” An accumulation of 100% was defined as the amount of actinomycin D which accumulated in the P-WEHI 164 cells in the absence of lipophilic drugs. Bars, SD.

Fig. 2. Effect of a mixture of lipophilic drugs on the accumulation of actinomycin D in act-R(C1.20)-WEHI 164 cells (clone 20). Cells were cultured for 4 h with actinomycin D and the individual drugs alone (●) or a mixture of the drugs (○). Drug accumulation was measured as described in “Materials and Methods,” and 100% drug accumulation was defined as the amount of actinomycin D which accumulated in the P-WEHI 164 cells in the absence of lipophilic drugs (●). Ami, 2.5 μg/ml amitriptyline; Prom, 2.0 μg/ml promethazine; Pen, 12.5 μg/ml pentazocine; Ver, 1.0 μg/ml verapamil; Prop, 5.0 μg/ml propranolol. Bars, SD.

rather than all five drugs (data not shown). The results suggest that the ability of the drugs to induce an increased accumulation of actinomycin D is additive.

Reversal of Multidrug Resistance by Lipophilic Drugs. In the initial screening (Table 1), the lipophilic drugs were tested for their ability to increase the accumulation of actinomycin D in MDR cells rather than for their ability to sensitize MDR cells to the cytotoxic effect of chemotherapeutic drugs. This was done since the former test system was simpler and more rapid. However, the most potent drugs were subsequently tested for their ability to sensitize the MDR cells to cytotoxicity. As one would expect, there was a positive correlation between the ability of the lipophilic drugs to increase the accumulation of actinomycin D in MDR cells and their ability to sensitize these cells to the cytotoxic effect of actinomycin D and doxorubicin. The concentrations of lipophilic drugs which induced an increased accumulation of actinomycin D in MDR cells and their ability to sensitize these cells to the cytotoxic effect of actinomycin D and doxorubicin. The concentrations of lipophilic drugs which induced an increased accumulation of actinomycin D in MDR cells (Fig. 1; Table 1) also sensitized these cells to the cytotoxic effect of actinomycin D and doxorubicin (Fig. 3). The fact that sensitization could even also be observed at somewhat lower concentrations (comparison of data in Fig. 3 with data in Fig. 2 and Table 1) may reflect that in the cytotoxicity assay the MDR cells were exposed to the lipophilic drugs for 48 h, whereas in the drug accumulation assay they were exposed to the drugs for only 4 h. The lipophilic drugs sensitized the MDR cells to doxorubicin and actinomycin D at concentrations where the lipophilic drugs alone did not induce a cytotoxic response in our cytotoxicity assay (Fig. 3). Similar results to those shown in Fig. 3 were also obtained with potassium canrenoate, chlor-
A. Promethazine  
B. Verapamil  
C. Amitriptyline  
D. Pethidine  
E. Pentazocine  
F. Propranolol

Fig. 3. Effect of lipophilic drugs on the sensitivity to doxorubicin and actinomycin D of P-WEHI 164 cells (parental) and act-R(C1.20)-WEHI 164 cells (clone 20). The cells were cultured in the presence of the indicated amounts of the different lipophilic drugs and either 5 µg/ml doxorubicin (O), 0.5 µg/ml actinomycin D (■ ■ ■ ■), or no chemotherapeutic drug (■ ■ ■ ■). The percentage cytotoxicity was measured after 48 h as described in “Materials and Methods.” Bars, SD.

promazine, lidocaine, biperiden, and phenytoin (data not shown).

Effect of Pentazocine on the Synergistic Cytotoxic Effect of Tumor Necrosis Factor and Actinomycin D on MDR Cells. TNF, a monocyte-produced protein which induces necrosis of tumors in animals, acts synergistically with actinomycin D in inducing a cytotoxic effect on various types of tumor cells (16, 17). This suggests the possible use of actinomycin D (or other chemotherapeutic drugs) in combination with TNF in cancer chemotherapy. As expected, 0.5 µg/ml actinomycin D potentiated the cytotoxic effect of TNF on the drug-sensitive parental cells, whereas it had only a very moderate effect on the MDR act-R(Cl.19)-WEHI 164 cells (Fig. 4, A and B). Pentazocine, however, sensitized the MDR cells to the synergistic cytotoxic effect of actinomycin D and TNF, in that the pentazocine-exposed MDR cells behaved similarly to the parental cells (Fig. 4C). Similar results were also obtained using erythromycin instead of pentazocine (data not shown). Pentazocine did not significantly increase the cytotoxic effect of actinomycin D and TNF on the drug-sensitive parental cells (data not shown). In the absence of actinomycin D, pentazocine protected the cells from killing by TNF (Fig. 4C), an observation we (10) and others (18) have also seen with verapamil. Although the act-R(Cl.19)-WEHI cells were somewhat less drug resistant than the act-R(Cl.20)-WEHI cells, the former were used in this experiment (Fig. 4) because they are, in contrast to the latter, relatively TNF sensitive.

DISCUSSION

A major obstacle to successful cancer chemotherapy is the emergence of MDR tumor cells. These cells are cross-resistant to a wide spectrum of lipophilic chemotherapeutic drugs. The phenomenon of multidrug resistance may imply that lipophilic compounds with low toxicity may be used to saturate and thereby inactivate the molecular system, presumably the P-glycoprotein, which protects MDR cells against lipophilic cytotoxic drugs. This hypothesis prompted us to test the effect of the relatively nontoxic antibiotic erythromycin on drug resistance. Erythromycin was shown to both induce an increased drug accumulation in MDR cells and reverse drug resistance (10, 11). Further support for the hypothesis are the present findings that at the concentrations tested, 19 (73%) of 26 lipophilic drugs (a) induced an increased accumulation of actinomycin D in MDR cells and/or (b) sensitized these cells to the cytotoxic effect of chemotherapeutic drugs. As expected, there was a good correlation between the ability of the lipophilic drugs to increase the accumulation of actinomycin D in MDR cells and their ability to sensitize these cells to the cytotoxic effect of chemotherapeutic drugs. As expected, there was a good correlation between the ability of the lipophilic drugs to increase the accumulation of actinomycin D in MDR cells and their ability to sensitize these cells to the cytotoxic effect of actinomycin D and doxorubicin. Three of the 26 drugs studied, propranolol, lidocaine, and chlorpromazine, have earlier been shown to modulate drug resistance (19–21); and this was also reported for promethazine while this study was carried out (22). However, since we were not aware of this at the time...
the drugs were chosen, these drugs were included when estimating the fraction of drugs which modulated drug resistance. Erythromycin and verapamil, however, were not included in our estimate since their effect on drug resistance was known to us beforehand, and they were used in this study only for comparative purposes. Trimethoprim, indomethacin, and phenytoin have previously been reported to have little, if any, effect on MDR (19, 23, 24). In this study these agents significantly increased the accumulation of actinomycin D in our MDR cells, and this is presumably due to the fact that we used higher concentrations than those applied in the previous studies.

Our results indicate that the ability to reverse drug resistance is in fact a relatively common property of lipophilic drugs. This presumably follows directly from the phenomenon of multidrug resistance which implies that a wide spectrum of structurally and functionally unrelated drugs are recognized and processed by the molecular system which protects the MDR cells against cytotoxic drugs. This notion is also consistent with earlier reports on various types of compounds that may partially or completely reverse drug resistance (12, 19–23, 25–30). Moreover, there appears to be a strong relationship between the lipophilic character of these compounds and their ability to modulate resistance (21). Of the agents known to reverse drug resistance, the calcium antagonist verapamil is perhaps the most studied (12). It was originally thought that verapamil reversal of drug resistance involved an effect on calcium channels, but recent evidence indicates that verapamil may in fact competitively bind to the P-glycoprotein (31). As a consequence, there is an increased accumulation of drugs in verapamil-treated MDR cells (12, 32–34), and the cells become sensitive to cytotoxic drugs.

Actinomycin D and TNF have a synergistic cytotoxic effect on tumor cells, which suggests the use of a combination of these two agents in cancer therapy. The clinical usefulness of this combination, however, may be hampered by the fact that there appears to be a correlation between the emergence of MDR and TNF-resistant cells. Three of 4 MDR WEHI 164 cell lines which we have developed were also relatively TNF resistant (10), and 5 of 6 clones [clone 19, the act-R(C1.19)-WEHI 164 cell line, being the exception] obtained by limiting dilution of the act-R-WEHI 164 cells were also TNF resistant.4 Moreover, Dollbaum et al. (35) recently reported a positive correlation between the sensitivity of malignant cells to TNF and their sensitivity to doxorubicin. Although actinomycin D and TNF have a synergistic cytotoxic effect even on the multidrug- and TNF-resistant cells, much higher concentrations of both TNF and actinomycin D are needed to kill these cells than to kill the drug-sensitive parental cells (10). This may, however, in part be counteracted by exposing MDR cells to lipophilic drugs which increase the accumulation of actinomycin D (Fig. 4). These results indicate that cellular accumulation of actinomycin D is necessary for its potentiating effect on TNF cytotoxicity. Consequently, the potentiating effect of actinomycin D on TNF cytotoxicity is not simply due to a direct effect of actinomycin D on the outer membrane, as has been suggested earlier (36, 37).

The amount of a lipophilic drug which was required to induce 100% accumulation of actinomycin D varied greatly from one drug to another. With propranolol, amitriptyline, potassium canrenoate, verapamil, and promethazine only about 10–20 μg/ml were required, with erythromycin as much as 600–750 μg/ml. This may possibly reflect differences in the affinities of the various lipophilic drugs to the P-glycoprotein and/or that the rate by which the drugs penetrate into cells varies. That a drug apparently must be lipophilic in order to reverse drug resistance may, similarly, be due to the P-glycoprotein having primarily high affinity for lipophilic compounds and/or that lipophilic compounds more easily penetrate into cells and thereby gain access to the binding site of the P-glycoprotein. There is also the possibility that some of the drugs may reverse drug resistance by other means than through binding to the P-glycoprotein. The lipophilic character of these drugs would enable them to interact with the cell membrane, and at the high drug concentrations used for some of the drugs such an interaction couldn’t happen.
might influence the uptake and/or efflux of chemotherapeutic drugs. The relatively high concentration on a weight basis of erythromycin which was required, however, may in part be explained by the fact that its molecular weight is 2-3 times greater than that of the other drugs.

The clinical usefulness of a lipophilic drug depends not only on its ability to reverse drug resistance at a low concentration but also on whether it has a low toxicity in vivo. Erythromycin and potassium canrenoate are in this respect of interest, since they are relatively well tolerated in vivo. Reversal of drug resistance with reduced in vivo toxicity may possibly be obtained by using a combination of two or more lipophilic drugs, since their ability to reverse drug resistance appears to be additive.

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